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Title:
Risk factors, activity monitoring and quality of life assessment in cats with early degenerative joint disease

RISK FACTORS, ACTIVITY MONITORING AND QUALITY OF LIFE ASSESSMENT IN CATS WITH EARLY DEGENERATIVE JOINT DISEASE

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1. ABSTRACT

Degenerative joint disease (DJD) is one of the most common causes of chronic pain in cats. Two studies were designed to identify risk factors for DJD in 6-year-old cats by examining prospective data from a longitudinal cohort study, and compare the activity profiles and quality of life of cats with (cases) and without (controls) early owner-reported signs of impaired mobility using orthopaedic examination, accelerometry and owner-completed questionnaires (Feline Musculoskeletal Pain Index (FMPI), VetMetrica).

Binomial logistic regression using backwards elimination identified four risk factors for increased owner-reported mobility impairment score in 6-year-old cats: entire neuter status at six months of age (OR=1.97, 95%CI 1.26–3.07), sustained trauma before six years of age (OR=1.85, 95%CI 1.3–2.6), outdoor access at six years of age (OR=1.67, 95%CI 0.96–2.9), and overweight/obese status at six years of age (OR=1.62, 95%CI 1.13–2.33). Case cats scored significantly lower than control cats for the FMPI ($p=0.003$) and the VetMetrica domain of comfort ($p=0.002$), but not vitality ($p=0.009$) or emotional wellbeing ($p=0.018$). Total pain ($p<0.0001$), crepitus ($p=0.002$) and thickening ($p=0.003$) scores were higher in case cats. Accelerometry differentiated cases from controls with a 90.9% accuracy.

Risk factor analysis demonstrated that obesity, outdoor access, and a history of trauma predispose cats to developing DJD, whereas neutering appears to decrease that risk. Changes in joint health as detected by orthopaedic examination and accelerometry reflected owner-reported mobility changes, differentiating cats with early DJD-related signs from healthy cats, whilst the VetMetrica comfort domain score indicated an impaired quality of life of cats with early DJD compared to healthy cats. Being able to recognise signs of mobility impairment earlier would allow interventions aimed at slowing DJD progression, thereby improving feline health and welfare. These findings have identified that orthopaedic examination, FMPI and accelerometry are effective in identifying early DJD-related mobility changes in cats.

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3. AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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4. TABLE OF CONTENTS

5. LIST OF TABLES

6. LIST OF FIGURES

7. LIST OF ABBREVIATIONS

-2LL	Log likelihood-ratio statistic
BC	Bristol Cats
BCS	Body condition score
CCL	Cranial cruciate ligament
CKD	Chronic kidney disease
C.L.A.W.S.	Cat Longitudinal Analysis of Welfare Study
CMI	Clinical metrology instruments
COX	Cyclooxygenase
CSOM	Client Specific Outcome Measures
Cx	Coxofemoral
df	Degrees of Freedom
DHA	Docosahexaenoic acid
DJD	Degenerative joint disease
DLH	Domestic long hair
DSH	Domestic short hair
EPA	Eicosapentaenoic acid
ETA	Eicosatetraenoic acid
EWB	Emotional wellbeing
FeLV	Feline leukaemia virus
FET	Fisher’s exact test
FPFF	Feline Physical Function Formula
FeSFV	Feline syncytia-forming virus
FHNE	Femoral head and neck excision arthroplasty
FET	Fisher's exact test

FIV	Feline immunodeficiency virus
FMPI	Feline Musculoskeletal Pain Index
FPFF	Feline Physical Function Formula
GLM	Green lipid mussel
HD	Hip dysplasia
HRQoL	Health related quality of life
IL	Interleukin
IQR	Interquartile range
LS	Lumbosacral
mAb	Monoclonal antibody
Mdn	Median
MI-CAT(C)	Montreal Instrument for Cat Arthritis Testing – Caretaker/Owner
MI-CAT(V)	Montreal Instrument for Cat Arthritis Testing – Veterinarian
MS	Mobility score
N/A	Not applicable
nBC	Non-Bristol Cats
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NSAIDS	Non-steroidal anti-inflammatory drugs
OBW	Owner Behaviour Watch
OR	Odds ratio
PPS	Pentosan polysulfate
PSGAG	Polysulfated glycosaminoglycan
PSW	Pressure-sensitive walkways
QoL	Quality of life

QST	Quantitative sensory testing
RTA	Road traffic accident
ROM	Range of motion
SFO	Scottish Fold osteochondrodysplasia
STT	Soft tissue trauma
S&P	Scale and polish
STMOAD	Structure-modifying osteoarthritis drugs
TNF-α	Tumour necrosis factor α
UK	United Kingdom
ZQB	Zamprogno Question Bank

1. INTRODUCTION

1.1 General Background

Feline degenerative joint disease (DJD) is one of the most common causes of chronic pain in cats, with prevalence increasing with age and prevalence estimates in radiographical studies ranging from 61% (Slingerland et al., 2011) to as high as 99% in cats of all ages (Lascelles et al., 2010b). Despite the high prevalence, little is known about risk factors predisposing cats to this condition, with increasing age being the only identified risk factor for feline DJD to date (Lascelles et al., 2010b, Slingerland et al., 2011). Similarly to humans where DJD has been shown to lead to reduced mobility and pain (Schaible, 2012), unpublished data suggest that approximately 40% of cats with radiographic DJD have an impaired mobility and experience pain secondary to DJD (Lascelles et al., 2010b). Cats are increasingly considered more of a family member than a pet (Turner, 2017), however some owners have a poor understanding of cat welfare needs (Rioja-Lang et al., 2019) and the impact of DJD on the cats' quality of life (QoL) has not been fully established.

Diagnosis of DJD requires combining information obtained from the owner, physical examination, and radiography, nevertheless it primarily depends on owners detecting changes in their cat's activity and behaviour, then seeking veterinary advice. Unfortunately, given the insidious onset and the subtlety of the clinical signs associated with DJD (Bennett and Morton, 2009, Clarke et al., 2005, Hardie et al., 2002, Klinck et al., 2012, Lascelles et al., 2007c) as well as the ability of cats to mask signs of disease (Gowan and Iff, 2016), it is likely that the disease is not recognised in a significant number of cats. Diagnosis is far from straightforward even in the consulting room as the stress that cats are subjected to when removed from their home environment can affect physiological parameters (Quimby et al., 2011), and possibly how cats exhibit pain within the consult room. In addition, cats may not allow clinicians to perform an orthopaedic examination or, even if they do, it is not always clear if resistance to joint palpation is due to pain or fear of handling (Clarke and Bennett, 2006, Lascelles et al., 2012). Radiographic findings may also not always correspond to orthopaedic findings, making feline DJD quite challenging to diagnose (Clarke and Bennett, 2006, Lascelles et al., 2007c).

Activity monitors have been used successfully to differentiate healthy cats from cats with DJD (Guillot et al., 2012, Lascelles et al., 2007c, Lascelles et al., 2008a), and these devices may also have the potential to objectively detect early signs of DJD in cats where the diagnosis has not yet been established.

1.2 The Feline Joint

1.2.1 Physiology

Joints are the connections between two bones that allow body parts to move, and are comprised of adjacent bones, subchondral bone, articular cartilage, ligaments, and tendons (Figure 1.1).

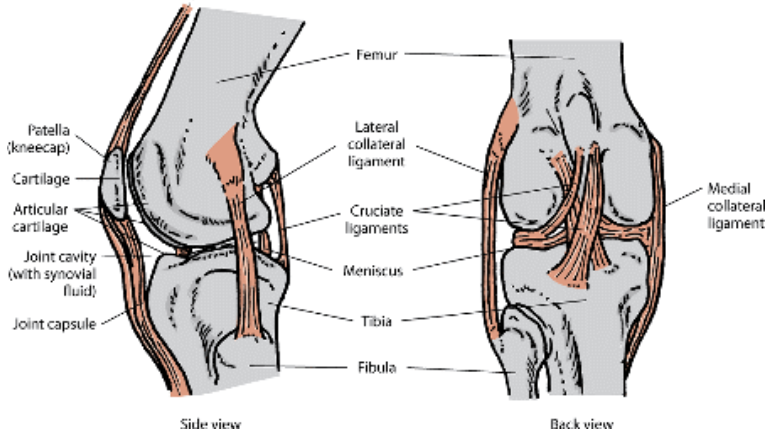

Figure 1.1: Components of a Feline Stifle Joint

(Taken from MSD Veterinary Manual, 2019)

Structurally, feline joints are divided into fibrous, cartilaginous, and synovial joints. Adjacent bones are joined by fibrous connective tissue in fibrous joints and by cartilage in cartilaginous joints. Cartilage is a more flexible type of connective tissue, allowing more movement between bones in cartilaginous than fibrous joints. Neither the bones of fibrous nor of cartilaginous joints have a joint cavity between them. On the other hand, synovial joints have a membrane that lines the joint and forms a cartilage-lined cavity filled with synovial fluid, a lubricating liquid secreted by the synovial membrane. Some synovial joints additionally have a fibrocartilage structure between the articulating surfaces of bones termed articular disc or meniscus, depending on its shape. The joint capsule connects the adjacent bones indirectly to each other, resulting in increased mobility. Synovial joints are further classified based on the shape of the bones' articulating surfaces into plane, hinge, pivot, ball-and socket, condyloid and saddle joints; each joint type allows for different levels of movement and rotation (Figure 1.2).

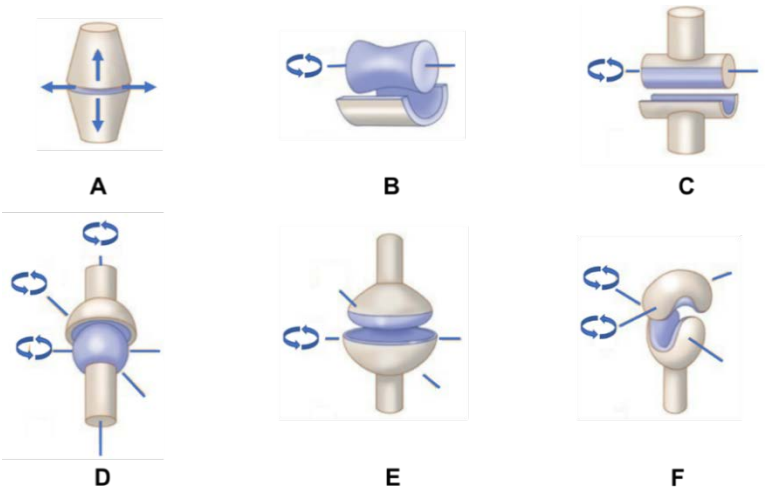

Figure 1.2: Schematic Illustration of the Six Types of Synovial Joints and the Types of Joint Movement.

A: Plane, B: Hinge, C: Pivot, D: Ball-and-socket E: Condyloid, F: Saddle

(Adapted from Study.com, 2019)

1.2.2 Joint Disorders

Joint disorders can be of inflammatory or non-inflammatory origin. Inflammatory joint disorders can be infectious or immune-mediated, affecting one (monoarthritis) or multiple (polyarthritis) joints. A plethora of bacterial, viral, fungal and rickettsial infectious agents is responsible for inflammatory joint disorders of infectious origin in cats (Lemetayer and Taylor, 2014). Non-inflammatory joint disorders are more common, and include developmental, degenerative, neoplastic, and traumatic causes. Irrespective of the instigating cause, all joint disorders are associated with varied degrees of pain and discomfort.

1.2.3 Physiology of Pain

Pain is classified as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk, 1994). Nociception refers to the physiologic component of pain consisting of the processes of transduction, transmission, and modulation of neural signals generated in response to an external noxious stimulus (Mathews et al., 2014). Pain is a complex

multi-dimensional experience that involves sensory, affective and functional components and is unique to the individual; not all animals may experience pain in response to nociception (Mathews et al., 2014).

Pain had traditionally been categorised as acute or chronic based on its duration, with chronic pain defined in human medicine as any pain that lasts more than three to six months (Merskey and Bogduk, 1994). More recently, the terms adaptive and maladaptive have been adopted to better describe pain (Woolf et al., 2004). Adaptive pain includes nociceptive and inflammatory pain (Figure 1.3). Nociceptive pain occurs in response to a noxious stimulus that may or may not cause tissue injury, whereas inflammatory pain follows tissue injury and is accompanied by an inflammatory response and inflammatory mediators that sensitise neural pathways. Both types of pain are reversible and considered protective.

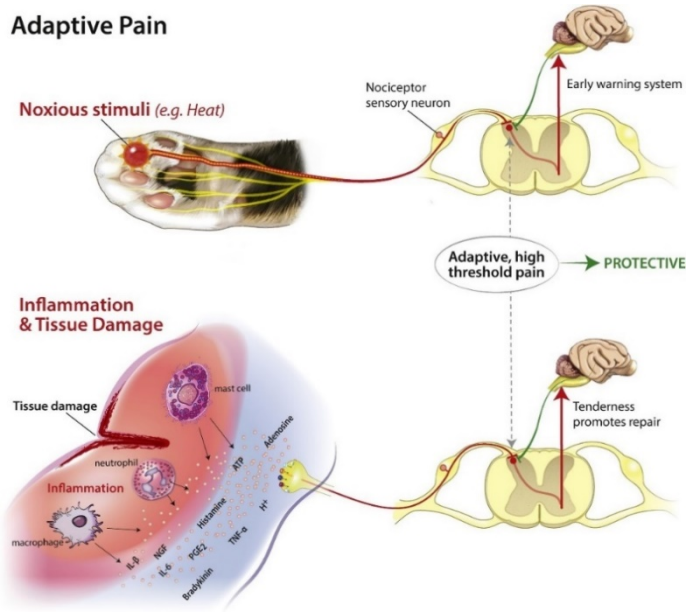

Figure 1.3: Schematic Illustration of Adaptive Pain

(Taken from Adrian et al., 2017)

Maladaptive pain, on the other hand, can develop from poorly treated adaptive pain and is the result of physical changes occurring in the brain and spinal cord (Figure 1.4). Maladaptive pain includes neuropathic pain, where direct damage to the neural tissue has occurred, and functional pain, where there is a dysfunction of the nociceptive system. Pivotal to the development of maladaptive pain are peripheral and central sensitisation (Adrian et al., 2017). In peripheral sensitisation, cell damage to an area causes the release of chemical mediators that sensitise nerve terminals or directly activate nociceptors, resulting in an increased sensitivity to afferent nerve stimuli. Central sensitisation involves the nervous system undergoing cellular wind-up then remaining autonomously in a high excitability state, thus lowering pain threshold. Two clinical phenomena are the hallmark of peripheral and central sensitisation: hyperalgesia and allodynia. Hyperalgesia is a stronger and prolonged pain response to a stimulus that would normally be painful, whereas allodynia is a pain response to a normally innocuous stimulus.

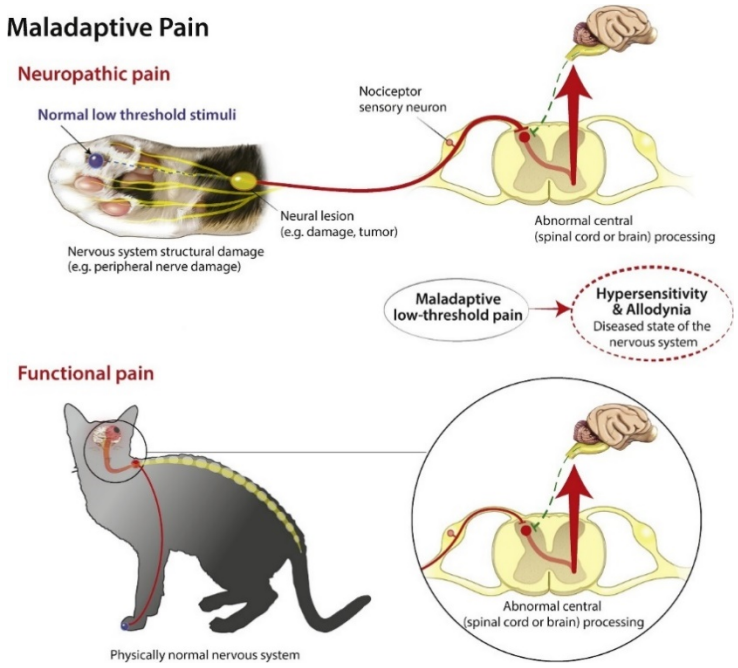

Figure 1.4: Schematic Illustration of Maladaptive Pain

(Taken from Adrian et al., 2017)

1.3 Feline Degenerative Joint Disease

1.3.1 Definition

Degenerative joint disease is a type of non-inflammatory joint disease that results from the gradual destruction of one or more joint components. This disease develops in all mammals and can affect synovial and cartilaginous, but not fibrous, joints.

Although the terms DJD and osteoarthritis have been used interchangeably, osteoarthritis refers to the degenerative process affecting synovial joints only. For the purposes of this thesis, the term appendicular DJD will be used to refer to degenerative pathology affecting synovial joints and the term axial DJD to refer to degenerative pathology affecting the spine.

1.3.2 Pathophysiology of Degenerative Joint Disease

The gradual loss of articular cartilage is considered one of the earliest markers of DJD progression (Eyre et al., 2006). Although there are repair mechanisms within the cartilage, it is likely that they decline with age which could partially explain the increased prevalence of DJD with age (Li et al., 2013). Since the mechanical properties of articular cartilage are directly linked to its biochemical composition, the weakening of its repair mechanisms also affects other joint components and destabilises the joint further, causing mechanical cartilage injury (Renberg, 2005). This results in cartilage ulceration, subchondral sclerosis and formation of subchondral cysts, periarticular osteophyte formation, interarticular mineralisation and periarticular tissue inflammation (Dedrick et al., 1993). Proposed cellular mechanisms in DJD are shown in Figure 1.5. Although there is a paucity of feline-specific studies investigating the pathophysiology of DJD, studies to date support these findings (Bennett et al., 2012a, Freire et al., 2014).

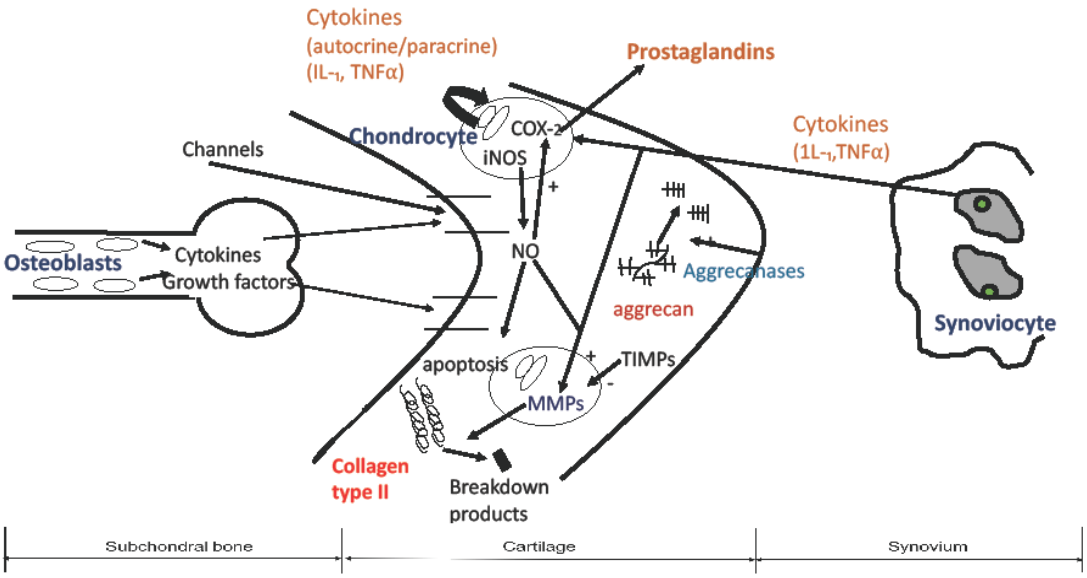

Figure 1.5: Cellular Mechanisms in Degenerative Joint Disease.

Cyclo-oxygenase (COX); interleukin (IL); inducible nitric oxide synthase (iNOS); matrix metalloproteinase (MMP); nitric oxide (NO); tissue inhibitor of metalloproteinase (TIMP); tumour necrosis factor α (TNF-α).
(Adapted from Abercromby et al., 2018)

1.3.2.1 Pathophysiology of Degenerative Joint Disease-related Pain

In humans, nerve growth factor (NGF) is considered a key molecule for nociceptor biology since clinical studies demonstrated that antibodies against NGF provided significant pain relief in patients with DJD (Schaible, 2012). Cytokines are also believed to play an important role; these are signalling proteins secreted by specific cells of the immune system that mediate inflammation among other things. Specifically, some cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β seem to be involved in inflammation and destruction in DJD (Schaible, 2012).

Clinical studies in human patients have documented that central sensitisation occurs in DJD and that DJD has a complex pain state, involving adaptive (nociceptive, inflammatory) as well as maladaptive (neuropathic) pain components (Schaible, 2012). Figure 1.6 displays a model of the joint nociceptive system indicating major processes likely to underlie DJD-related pain.

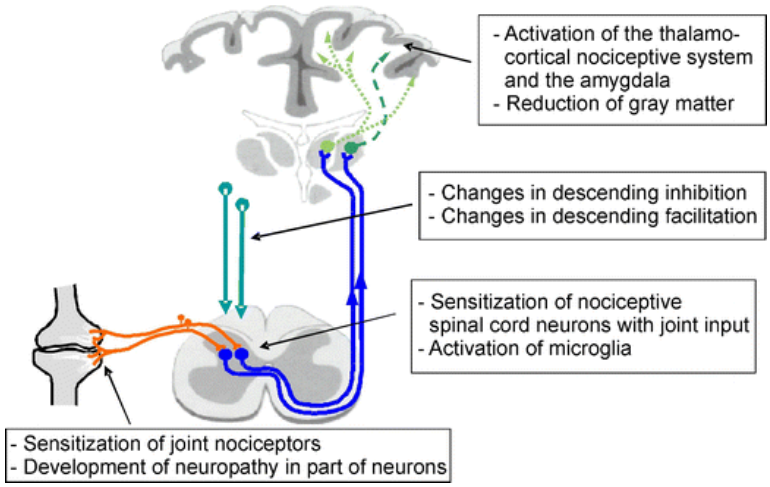

Figure 1.6: Model of the Nociceptive System of the Joint and Major Processes Likely to Underlie DJD-related Joint Pain

(Taken from Schaible, 2012)

The pathophysiology of DJD-related pain has not been elucidated in cats, however DJD has been established as a clinical condition that results in long-term pain in this species (Robertson and Lascelles, 2010). Central sensitisation has also been shown to occur in cats with DJD (Guillot et al., 2013). Consequently, multimodal analgesic therapy that takes advantage of different modes as well as sites of action of analgesic drugs is advocated.

1.3.3 Prevalence

Multiple studies have investigated the prevalence of radiographic DJD in cats. Appendicular DJD has been studied more extensively, with prevalence ranging from 22% to 74% and 61% to 91% in retrospective and prospective studies investigating all joints, respectively (Table 1.1). Bilateral disease is a common finding, occurring in 46% to 91% of cats with appendicular DJD depending on if it was estimated based on radiography (Godfrey and Vaughan, 2018, Kimura et al., 2020) or combined orthopaedic and radiographic findings (Clarke and Bennett, 2006, Godfrey, 2005, Lascelles et al., 2010b, Slingerland et al., 2011).

Table 1.1: Summary Findings of the Reported Prevalence of Radiographic Appendicular Feline Degenerative Joint Disease

Study Design	Joints studied	Mean age (years)	% of cats with DJD in ≥ 1 joint	Most commonly affected joint	Reference
PC	Cx	2.5	19	-	(Langenbach et al., 1998)
RS	Cx	2.8	6.3	-	(Keller et al., 1999)
RCS	Stifles	3.3	68	-	(Loughin et al., 2006)
RS	All	15.2	64	Elbow (17%)	(Hardie et al., 2002)
RS	All	6.5 (10.2 median)	16.5	Cx (51%)	(Clarke et al., 2005)
RS	All	8.2	22	Elbow (21.8%)	(Godfrey, 2005)
RS	All	10.1	57	Cx (34%), Elbow (24%), Shoulder (21%), Stifle (19%), Tarsus (17%), Carpus (3%)	(Godfrey, 2008)
PC	All	11 (median)	-	Elbow (45%), Cx (38%)	(Clarke and Bennett, 2006)
PC	All	9.5	91	Cx (65%), Stifle (50%), Tarsus (40%), Elbow (35%)	(Lascelles et al., 2010b)
PC	All	11	61	Shoulder, Elbow, Cx , Tarsus	(Slingerland et al., 2011)
RS	All	7.8	74	Stifle (53%), Cx (46%), Elbow (42%), Tarsus (30%)	(Godfrey and Vaughan, 2018)
RS	All	9.8[+]	74.3	Elbow, Stifle	(Kimura et al., 2020)

Coxofemoral (Cx); Degenerative Joint Disease (DJD); Prospective cohort (PC); Retrospective case series (RCS); Retrospective survey (RS). [+]*Median.*

With regards to axial DJD, prevalence ranges from 21% to 80% in retrospective studies and from 55% to 92% in prospective studies (Table 1.2). The thoracic and lumbosacral regions are the most commonly and most severely affected areas, respectively.

Table 1.2: Summary Findings of the Reported Prevalence of Radiographic Axial Feline Degenerative Joint Disease

Study Design	Mean age (years)	% of cats with axial DJD	Most commonly affected area	Most severely affected area	Reference
RS	Unknown (older)	58	Thoracic (T_{7-8})	-	(Beadman, 1964)
RS	15	80	-	Lumbosacral	(Hardie et al., 2002)
RS	6.5	21	Thoracic ($T_{6-7, 9-10}$)	Lumbar	(Clarke et al., 2005)
PC	11	-	Thoracic	Thoracic	(Clarke and Bennett, 2006)
PC	14	92	Thoracic	-	(Lascelles et al., 2007b)
PC	9.5	55	Thoracic	Lumbosacral	(Lascelles et al., 2010b)
RS	9.8^{+}	40.6	Lumbosacral	Lumbosacral	(Kimura et al., 2020)

Degenerative Joint Disease (DJD); Prospective cohort (PC); Retrospective survey (RS). $^{+}$Median

Prevalence differences between retrospective and prospective studies most likely reflect different study designs. Estimating DJD prevalence based on retrospective radiographical studies for example is difficult for several reasons. Firstly, the age between study populations differs greatly and is not equally distributed, which makes drawing firm conclusions difficult. In addition, due to the retrospective nature of these studies, not all radiographs were obtained with the intent to study the joints, some views were missing, and sometimes routine thoracic or abdominal radiographs were used to estimate prevalence. Another confounding factor in comparing results from different studies irrespective of their design is the fact that each study used different radiographical criteria to grade DJD according to severity (Clarke and Bennett, 2006, Clarke et al., 2005, Godfrey, 2005, Hardie et al., 2002, Slingerland et al., 2011).

1.3.4 Causes

Feline DJD is classified as primary or secondary depending on the aetiology (Table 1.3).

Table 1.3: List of Recognised and Postulated Primary and Secondary Causes of Feline Degenerative Joint Disease

Primary	• Scottish Fold osteochondrodysplasia (Gandolfi et al., 2016, Malik et al., 1999) • Mucopolysaccharidosis VI (Crawley et al., 2003, Macri et al., 2002) • Age-related cartilage degeneration (Lascelles, 2010)
Secondary	• Congenital / Developmental o Hip dysplasia (Keller et al., 1999, Langenbach et al., 1998, Loder and Todhunter, 2018) o Patellar luxation (Langenbach et al., 1998, Loughin et al., 2006, Smith et al., 1999) o Elbow dysplasia (Freire et al., 2014, Freire et al., 2011, Staiger and Beale, 2005) o Elbow luxation (Rossi et al., 2003, Valastro et al., 2005)
	• Traumatic o Cranial cruciate ligament injury (Harasen, 2005, Herzog et al., 1993, Leumann et al., 2019, Wessely et al., 2017, Wu et al., 2000) o Other trauma (Clarke and Bennett, 2006, Clarke et al., 2005, Godfrey, 2005, Hardie et al., 2002, Johnston, 1997)
	• Nutritional – Hypervitaminosis A (Polizopoulou et al., 2005)
	• Endocrine – Hypersomatotropism (Peterson et al., 1990, Wassenaar et al., 2009)
	• Neoplastic o Synovial osteochondromatosis (Tan et al., 2010, Tas et al., 2013) o Osteosarcoma (Godfrey, 2005)
	• Immune-mediated (Gao et al., 2013, Lemetayer and Taylor, 2014) o Erosive polyarthropathies ▪ Feline periosteal proliferative polyarthritis ▪ Feline rheumatoid-like arthritis o Non-erosive polyarthropathies ▪ Primary or idiopathic ▪ Secondary (Reactive polyarthritis, systemic lupus erythematosus)
	• Infectious (Lemetayer and Taylor, 2014) o Mycoplasma spp (Liehmann et al., 2006, Moise et al., 1983, Zeugswetter et al., 2007) o Bartonella spp (Tomas et al., 2015) o Histoplasma capsulatum (Wolf, 1987) o Cryptococcus neoformans (Tisdall et al., 2007) o Feline leukaemia virus (Oohashi et al., 2010, Pedersen et al., 1980) o Feline syncytia-forming virus (Inkpen, 2015, Pedersen et al., 1980)

Primary or idiopathic DJD is suggested to occur without an apparent initiating cause. Scottish Fold osteochondrodysplasia (SFO) and mucopolysaccharidosis are considered primary forms of DJD in cats. Briefly,

SFO is a dominantly inherited disorder which results from a generalised defect in cartilage metabolism, causing malformations in the distal forelimbs, distal hindlimbs and tail as well as progressive appendicular joint destruction (Gandolfi et al., 2016, Malik et al., 1999). Mucopolysaccharidosis VI is a recessively inherited disease that has been identified in Siamese and domestic shorthair (DSH) cats, with affected cats exhibiting malformations of the skull, vertebrae and joints, resulting in arthropathies (Crawley et al., 2003, Macri et al., 2002). Nevertheless, neither SFO nor mucopolysaccharidosis are commonly encountered in practice, and most cases with DJD have no obvious initiating cause. This has been termed age-related cartilage degeneration (Lascelles, 2010) and, as primary DJD is a diagnosis of exclusion, it is possible that factors that have yet to be recognised are responsible for the occurrence of DJD in these cats. Secondary DJD occurs as a result of a specific disease process and a plethora of recognised and postulated factors of congenital, traumatic, nutritional, endocrine, infectious, and immune-mediated origin have been linked with its development.

Hip dysplasia (HD) is a developmental disease that has been established to result in secondary DJD (Keller et al., 1999, Langenbach et al., 1998, Loder and Todhunter, 2018). It has a reported incidence ranging from 7% to 32%, with secondary DJD reported in 60% to 95.5% of cases and with Maine Coon, Persian and Himalayan being the most commonly affected breeds (Table 1.4).

Table 1.4: Summary Findings of the Reported Prevalence of Feline Hip Dysplasia With/Without Degenerative Joint Disease

Study Design	Number of cats	Mean age (years)	Breed	Cats with HD	Cats with HD + DJD	Reference
PC	78	2.5	22% DSH, 78% purebred	25 (32%)	15 (60%)	(Langenbach et al., 1998)
RS	684	2.8	88% DSH, 12% purebred	45 (6.6%)	43 (95.5%)	(Keller et al., 1999)
RS	2548	0.5 – 2.5	Maine Coon	635 (24.9%)	-	(Loder and Todhunter, 2018)

Degenerative Joint Disease (DJD); Domestic shorthair (DSH); Hip Dysplasia (HD); Prospective cohort (PC); Retrospective survey (RS).

Patella luxation is another developmental disease that has been established as a cause of secondary DJD in both pedigree and non-pedigree cats (Smith et al., 1999). In a more recent study, variable degrees of DJD were seen in 64% of stifle joints with patella luxation, and the cats that exhibited the most severe DJD also had a grade 4 luxation, which could suggest that the severity of DJD in the stifle increases in response to the increase in patella luxation severity (Loughin et al., 2006). In the same study, an association was also found between HD and patellar luxation, with 43% of cats suffering from both conditions. This substantiates the findings of a previous study where 24% of cats had both conditions and cats were three times more likely to suffer from both than from either condition alone (Langenbach et al., 1998).

Elbow dysplasia has also been suggested to result in secondary DJD (Staiger and Beale, 2005). However, in subsequent studies evaluating elbow DJD neither fractured medial coronoid process nor osteochondritis dissecans, the most common forms of elbow dysplasia in dogs, were shown to play a role in the development of feline DJD (Freire et al., 2014, Freire et al., 2011). Elbow luxation is unlikely to be a cause of secondary DJD based on the only two published case reports (Rossi et al., 2003, Valastro et al., 2005).

Trauma has been historically postulated to be a cause of DJD (Hardie et al., 2002, Johnston, 1997) and has been suggested to be a secondary cause of DJD in both retrospective and prospective studies of cats with DJD (Clarke and Bennett, 2006, Clarke et al., 2005, Godfrey, 2005). However, to the researcher's knowledge, the occurrence of DJD following joint trauma has not been evaluated. Transection of the cranial cruciate ligament (CCL) has been shown to lead to secondary DJD in experimental models (Herzog et al., 1993, Leumann et al., 2019, Wu et al., 2000), but the aetiopathogenesis of feline CCL disease has not been elucidated. One case study with 17 cats suggested both a traumatic and a degenerative aetiology, although only a single CCL was examined histologically (Harasen, 2005), whereas a more recent case study examined 19 ruptured CCL and did not find any histological evidence to support a degenerative process (Wessely et al., 2017).

Hypervitaminosis A has been reported in cats whose diet predominantly consists of liver and is rarely seen nowadays since most cats are mainly fed nutritionally complete commercial diets (Polizopoulou et al., 2005).

The increased risk of developing DJD secondarily to hypersomatotropism (acromegaly) is well recognised in human patients, with DJD-related clinical signs being present in 50% to 70% of patients at diagnosis (Wassenaar et al., 2009). Secondary DJD in acromegalic cats has only been reported in one case study (Peterson et al., 1990), with 42.9% of cats with acromegaly exhibiting DJD-related radiographical changes in their shoulder, elbow, carpus, stifle, digits and spine. Although this study reported the concurrent presence of both disease processes, the causal effect was not evaluated. Consequently, since all study cats were middle-aged or older, it is possible that the cats were suffering from age-related cartilage degeneration rather than secondary DJD as a result of acromegaly.

With regards to neoplasia as a secondary cause of DJD, another suggested cause is synovial osteochondromatosis. However, these benign lesions reportedly occur less likely as a primary entity, but more commonly represent a degenerative condition of synovial epithelium near joints affected by DJD (Tan et al., 2010, Tas et al., 2013). Appendicular DJD was also reported secondarily to a single case of osteosarcoma in a retrospective study (Godfrey, 2005), however an association between joint malignant neoplasia and secondary DJD has not been reported elsewhere to the researcher's knowledge.

An immune-mediated aetiopathogenesis has been proposed for several forms of secondary DJD. These were initially termed 'chronic progressive arthritis' (Pedersen et al., 1980), but then it became clear that different forms existed (Bennett and Nash, 1988). More recently, differences were found in the immune responses between cats with DJD and age-matched controls, suggesting that an impaired immune response could cause and/or exacerbate DJD (Gao et al., 2013). Immune-mediated polyarthropathies are presently classified as erosive or non-erosive based on clinical and radiographic findings (Lemetayer and Taylor, 2014). Erosive polyarthropathies include feline periosteal proliferative polyarthritis and feline rheumatoid-like arthritis, whereas non-erosive polyarthropathies occur as a primary or idiopathic disorder, secondarily to antigenic stimulation (reactive polyarthritis) or as a feature of systemic lupus erythematosus (Gao et al., 2013).

Infectious agents such as *Bartonella spp* (Tomas et al., 2015), *Mycoplasma gatae (Moise et al., 1983, Zeugswetter et al., 2007)*, *Mycoplasma felis* (Liehmann et al., 2006), *Histoplasma capsulatum* (Wolf, 1987), *Cryptococcus neoformans* (Tisdall et al., 2007), Feline leukemia virus (Oohashi et al., 2010, Pedersen et al., 1980) and Feline syncytia-forming virus (Inkpen, 2015, Pedersen et al., 1980) have also been postulated to be instigating factors in the development of secondary DJD. Bacterial arthritis as a result of direct inoculation with bacteria or haematogenous spread has been occasionally reported in the literature as a cause of DJD in cats (Lemetayer and Taylor, 2014), with Godfrey (2005) first reporting appendicular DJD occurring secondarily to osteomyelitis. Contrary to a study in dogs where an association between *Bartonella spp*. seropositivity and disease states was established (Henn et al., 2005), *Bartonella spp.* seropositivity was associated with decreased severity of DJD in a recent study (Tomas et al., 2015).

1.3.5 Risk Factors

Age is the only identified risk factor for feline DJD (Lascelles et al., 2010b, Slingerland et al., 2011), with one prospective study showing that the expected total DJD score (which reflects the severity of the disease) increased by approximately 14% for each 1-year increase in a cat's age (Lascelles et al., 2010b). Only one study found no association between age and DJD severity (Hardie et al., 2002); however, this study's population included cats exclusively over the age of 12 which may have resulted in the inability to observe this association.

The association between obesity and the development of DJD has been established in humans (Vina and Kwoh, 2018) and in dogs (Zoran, 2010). It has been postulated that obesity is a risk factor for the development of secondary DJD in cats; nevertheless, a causal relationship has yet to be shown. Overweight cats were more likely to be diagnosed with a locomotor disease in a retrospective study (Ohlund et al., 2018), whereas overweight and obese cats were, respectively, approximately three and five times more likely to develop lameness requiring veterinary care in a prospective study of approximately 1,500 cats (Scarlett and Donoghue, 1998). In the later study, it was speculated that cartilage damage and appendicular DJD could have been caused

by excess bodyweight or a generalised abnormality in lipid metabolism which is in line with the proposed biomechanical mechanisms in humans (Guilak, 2011) and dogs (Marshall et al., 2009). Unfortunately, the cause of lameness and, consequently, a possible association with DJD was not evaluated. No significant association between weight or BCS and appendicular DJD severity (Slingerland et al., 2011) or radiographic signs of DJD (Clarke et al., 2005) was found in two retrospective studies. In a prospective study, bodyweight and BCS were not associated with appendicular DJD either, but a negative association was found with axial DJD severity (Lascelles et al., 2010b). The authors suggested this could be explained by the effect of age on bodyweight since older cats have been demonstrated to have increased maintenance energy requirements which results in a decreased weight and BCS (Laflamme, 2005). Apart from increasing age, none of the other proposed variables were found to be significantly associated with the development of DJD (Table 1.5).

Table 1.5: Previously Investigated Risk Factors for Feline Degenerative Joint Disease

Authors / Criteria	Scarlett and Donoghue, 1998 [PC]	Hardie et al., 2002 [RS]	Clarke, 2005 [RS]	Lascelles et al., 2010b [PC]	Slingerland, 2011 [PC]	Godfrey and Vaughan, 2018 [RS]	Ohlund et al., 2018 [C]
Age		✓	✓	✓	✓	✓	
BCS	✓		✓	✓	✓		✓
Sex		✓	✓	✓		✓	
Neuter status						✓	
Breed		✓			✓		
Time spent outdoors		✓		✓			
Vaccination status		✓		✓			
FeLV/FIV status		✓		✓			
Use of flea/tick prevention				✓			

Body Condition Score (BCS); Feline leukaemia virus (FeLV); Feline immunodeficiency virus (FIV).
Study design marked as Cross-sectional (C); Prospective cohort (PC); Retrospective survey (RS).

Hardie and others (2002) did not find any association between DJD severity and a plethora of diseases, such as diabetes mellitus, hyperthyroidism, neoplasia (other than thyroid neoplasia), dental disease, gastrointestinal disease, urinary tract disease, cardiovascular disease, ocular disease, and skin disease. Notwithstanding the lack of association between neurological signs and appendicular DJD severity, there was a significant association between neurological signs and axial DJD severity.

A number of haematologic, serum biochemical and urinalysis variables were initially found to be significant predictors of DJD and DJD severity when considered individually (Lascelles et al., 2010b). None of these variables were however significantly associated with the presence of DJD or DJD severity once age was accounted for. Nevertheless, the authors speculated that some of the investigated variables may be associated with DJD and that the same pathological process may be observed in DJD and, for example, chronic kidney disease. Interestingly, a recent retrospective study reported that approximately 70% of cats with DJD had concurrent CKD and that concurrent CKD was associated with higher levels of feline DJD pain, supporting the notion of a common pathway (Chiu et al., 2019). This newer finding could also possibly explain the very strong association found between lipase and DJD in the study by Lascelles and others (2010b), since the decreased renal function observed in CKD would also decrease lipase clearance. Dental disease is another chronic inflammatory process associated with age, and an independent association between the severity of dental disease and the development of CKD has been found (Finch et al., 2016). This additional finding further endorses the concept of a common pathway linking chronic inflammatory processes such as dental disease, CKD and DJD.

1.3.6 Clinical Signs

Domestic cats have retained the instinctive behaviour of wild cats to hide overt signs of pain and disease from potential predators (Gowan and Iff, 2016). Although this has resulted in DJD-associated clinical signs being

subtle, owners are generally able to recognise them when appropriately directed by the veterinary surgeon (Bennett and Morton, 2009b, Klinck et al., 2012).

Owner observations are extremely useful in veterinary medicine as they provide veterinary surgeons with insight on the cat's mobility and behaviour in their natural environment, away from the stress associated with visiting the clinic. Lameness is the most cardinal sign of DJD in dogs (Pettitt and German, 2015), however it is rarely the presenting complaint in cats as it is only reported in 4% to 17.5% of cats with DJD (Clarke et al., 2005, Hardie et al., 2002). This may be explained by the fact that bilateral disease is quite common in cats with DJD, and therefore the gait asymmetry that is needed for lameness to be observed is not present. It is also possible that lameness is not a major feature of feline DJD. Indeed, no lameness was observed during the 1-year duration of an experimental study involving a feline cruciate transection model of DJD despite progression of radiographic DJD (Suter et al., 1998). Studies to date agree that the most common owner-reported changes seen in cats suffering from DJD-associated pain relate to mobility (altered jumping frequency and height, altered stair use, altered gait), followed by decreased activity levels, decreased grooming as well as changes in social behaviour and litter box use (Bennett and Morton, 2009, Klinck et al., 2012, Lascelles et al., 2007c, Slingerland et al., 2011). Cats with DJD also display increased vocalisation, resistance to handling, changes in play and hunting behaviour (Hardie et al., 2002, Klinck et al., 2012).

1.3.7 Diagnostic Methods

Diagnosis of DJD requires combining information obtained from the owner, physical examination, and radiography (Figure 1.7).

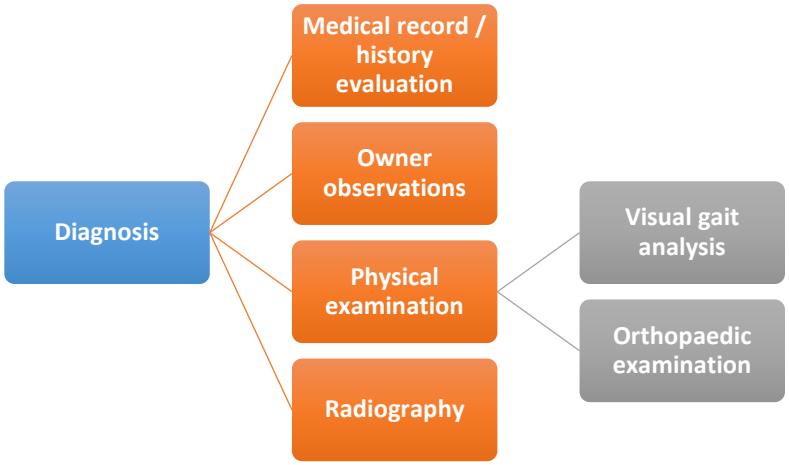

Figure 1.7: Multidimensional Approach to Diagnosing Degenerative Joint Disease

1.3.7.1 History Evaluation and Owner Observations

The index of suspicion for the presence of DJD may be raised if veterinary surgeons identify a) known primary or secondary causes of DJD whilst evaluating a cat's medical record, or b) previously described DJD-related clinical signs during history taking.

1.3.7.2 Physical Examination

In addition to obtaining information from the owner about changes in the cat's mobility and behaviour, veterinary surgeons should also perform a physical examination. The stress that cats are subjected to when removed from their home environment and taken to the veterinary practice has been shown to affect physiological parameters (Quimby et al., 2011). This may also affect how cats exhibit pain within the consult room and thereby make the interpretation of the orthopaedic examination more difficult. Visual gait analysis involves subjectively observing an animal's gait and should ideally be undertaken before the orthopaedic examination takes place. Nevertheless, a low agreement was shown between visual and objective gait analysis in dogs with orthopaedic disease (Quinn et al., 2007), disputing its diagnostic value. In cats, it is likely that the

agreement is even lower, not only due to the high prevalence of bilateral disease and resulting lack of gait asymmetry, but also due to the unwillingness of the species to walk within the consult room.

An orthopaedic examination involves manipulating individual joints and assessing the degree of pain, crepitus, effusion and thickening associated with each joint (Lascelles et al., 2012). Resistance to joint palpation and manipulation is a common finding in cats with DJD; however, this may often be due to fear of handling, which would result in overestimating the number of clinically affected joints. Conversely, some cats may not tolerate the orthopaedic examination and their reaction may not necessarily reflect that the assessed joint was painful (Clarke and Bennett, 2006, Lascelles et al., 2012), which would in turn result in underestimating the number of clinically affected joints.

1.3.7.3 Radiography

Computed tomography and magnetic resonance imaging are powerful imaging modalities but are not routinely used to confirm the presence of DJD. Radiography has historically been performed to support orthopaedic examination findings, further raising the degree of suspicion, or confirming the presence of DJD.

Nevertheless, radiographic findings may not always correspond to orthopaedic findings and vice versa. Radiographic findings agreed with orthopaedic findings in 66% of joints with DJD in one prospective study (Clarke and Bennett, 2006), whereas in another prospective study only 33% of joints with radiographic signs of DJD were found to be painful on orthopaedic examination (Lascelles et al., 2007c). Nevertheless, Lascelles and others (2012) suggested that absence of pain, crepitus, effusion or thickening in conjunction with normal goniometry (joint angle measurement) can be used to confidently rule out the presence of radiographic DJD and, at the same time, detecting crepitus, effusion and thickening will increase the likelihood of radiographic DJD being present.

With regards to the radiographic criteria of feline DJD, Allan (2000) suggested that the radiographic signs of appendicular DJD in cats are similar to those seen in dogs. Following this, Hardie and others (2002) used a

scoring system that considered both the presence and the severity of DJD-associated radiographic features (Morgan, 1999). The same criteria were used in both studies by Clarke (Clarke and Bennett, 2006, Clarke et al., 2005). In his earlier studies (Godfrey, 2008, Godfrey, 2005), Godfrey considered appendicular DJD present if some of the criteria described by Hardie and others were present. A few years later, it was suggested that the radiographic appearance of feline DJD differs from canine DJD, and a group of board certified veterinary radiologists and surgeons established their own criteria for the evaluation of radiographic signs of feline appendicular DJD (Freire et al., 2011, Lascelles et al., 2010b). The same criteria were later used by Godfrey and Vaughan (2018), although before that Slingerland and others (2011) chose to use some of the criteria suggested by Hardie and others (2002) instead. The different radiographic criteria used to describe the radiographic appearance of appendicular DJD are listed in Table 1.6.

Table 1.6: Summary of Radiographic Appearance of Appendicular Feline Degenerative Joint Disease

Authors / Criteria	Allan, 2000	Hardie et al., 2002	Godfrey, 2005	Clarke et al., 2005	Clarke and Bennett, 2006	Godfrey, 2008	Lascelles et al., 2010	Freire et al., 2011	Slingerland, 2011	Godfrey and Vaughan, 2018
Osteophytes		✓	✓	✓	✓	✓	✓	✓		✓
Enthesophytes	✓✝	✓		✓	✓		✓	✓		✓
Periarticular new bone formation		✓	✓			✓			✓	
New bone formation (tarsal joint)							✓	✓	✓	
Joint-associated mineralisation		✓					✓	✓	✓¥	✓
Intra-articular mineralisation	✓	✓		✓	✓		✓	✓	✓	✓
Sclerosis	✓	✓	✓✳	✓	✓	✓	✓	✓	✓	✓
Joint effusion	✓	✓					✓	✓		✓
Subchondral bone erosions/cysts	✓	✓					✓	✓		✓
Subluxation coxofemoral joint							✓	✓		

✝*Described as periarticular bone formation within the text.* ¥*Described as soft tissue mineralisation within the text.* ✳*Described as increased subchondral bone density within the text.*

With regards to the radiographic features of axial DJD, these have not been researched as extensively. Morgan's scoring system was used in two studies (Clarke et al., 2005, Hardie et al., 2002) before the same group that established radiographic criteria in feline appendicular DJD did so for axial DJD (Lascelles et al., 2010b). The different radiographic criteria used to describe the radiographic appearance of axial DJD are listed in Table 1.7.

Table 1.7: Summary of Radiographic Appearance of Axial Feline Degenerative Joint Disease

Authors / Criteria	Hardie et al., 2002	Clarke et al., 2005	Lascelles et al., 2010
Osteophytes	✓	✓	✓
Enthesiophytes	✓	✓	
Spondylosis			✓
Disc-associated degeneration	✓	✓	✓✦

✦*Disc-associated degeneration includes end-plate sclerosis, erosion, disc mineralisation and narrowing.*

1.4 Chronic Pain Assessment in Feline Degenerative Joint Disease

All animals experience pain; however, response to pain depends on the animal's age and species (Epstein et al., 2015). Pain assessment in cats with DJD is challenging not only due to the species' ability to mask signs of pain, but also because pain-related behavioural changes such as aggression, avoidance of handling and lack of responsiveness to human attention (Lascelles and Waterman, 1997) are sometimes considered part of the natural ageing process by owners (Merola and Mills, 2016).

1.4.1 Subjective Outcome Measures of Chronic Pain

1.4.1.1 Clinical Metrology Instruments

Clinical metrology instruments (CMI) are tools that can be used for the assessment of pain and take the form of questionnaires. There are two types of CMIs, those that are completed by owners and those that are completed by veterinary surgeons.

Owner assessments comprise the mainstay of chronic pain assessment in veterinary medicine given the inability of animals to assess and self-report pain. One of the main advantages of using CMIs is that they facilitate assessment in the home environment where cats are not subjected to the stress of visiting the clinic. In addition, they are easy to use and cost effective. There are several CMIs aimed at owners available for the assessment of chronic pain in cats suffering from DJD: the Zamprogno Question Bank (ZQB), the Feline Musculoskeletal Pain Index (FMPI), the Owner Behaviour Watch (OBW), the Feline Physical Function Formula (FPFF), the Montreal Instrument for Cat Arthritis Testing – Caretaker/Owner (MI-CAT(C)) and the Client Specific Outcome Measures (CSOM).

The ZQB contains items identified as essential after the authors showed that behaviours linked to activity differed between cats with DJD and DJD-free cats (Zamprogno et al., 2010); this was later used to construct the FMPI. The FMPI (Appendix A) is a general subjective outcome measure where the ability of cats to perform 17

activities compared to a normal cat is rated by their owners on a Likert scale; it has been shown to have discriminatory validity and good repeatability (Benito et al., 2013a, Benito et al., 2013b, Gruen et al., 2015). This CMI has been used in clinical studies evaluating pain relief for DJD-associated pain (Gruen et al., 2014, Gruen et al., 2016), as well as the management of pantarsal arthrodesis (Alza Salvatierra et al., 2018), tibial fractures (Craig et al., 2018) and cranial cruciate ligament disease (Boge et al., 2019). The OBW is also a general subjective outcome measure where the ability of cats to perform activities assigned to four domains (mobility, activity, grooming, temperament) is compared to a normal cat, and their overall problem severity is rated by their owners on a Likert scale. This CMI was constructed to evaluate treatment response in cats with DJD receiving meloxicam (Bennett and Morton, 2009) and was later used to evaluate treatment response in cats with DJD receiving both meloxicam and glucosamine/chondroitin sulphate (Sul et al., 2014). The MI-CAT(C) is a newer general subjective outcome measure that contains 38 items relating to a cat's ability, behaviour and physical condition; these are again rated by owners on a Likert scale (Klinck et al., 2018a). Following content validation and piloting (version one), the researchers conducted a randomised, blinded, placebo-controlled study, producing version two. The FPFF is another general subjective outcome measure which was based on the OBW and has been evaluated in one study (Stadig et al., 2019). The CSOM on the other hand is an individualised subjective outcome measure where three activities are selected by owners and the ability of their cats to perform them is rated on a Likert scale (Benito et al., 2013a, Gruen et al., 2015, Lascelles et al., 2007c). This CMI has been used exclusively to evaluate the DJD in cats, and in particular pain relief for DJD-associated pain (Gruen et al., 2017b, Gruen et al., 2014, Gruen et al., 2016, Guedes et al., 2018b) and a therapeutic diet (Lascelles et al., 2010a). Only FMPI, MI-CAT(C) and CSOM have been tested in blinded, placebo-controlled studies (Gruen et al., 2014, Gruen et al., 2015, Gruen et al., 2016, Lascelles et al., 2007c), with Klinck and others (2018a) suggesting that further refinement and testing in a larger sample of cats is necessary for MI-CAT(C). The results of a more recent study compared different CMIs (ZQB, OBW, FPFF, FMPI) and suggested that FMPI is the best CMI to use in a clinical setting (Stadig et al., 2019). Indeed, the FMPI is also the researcher's

preferred general CMI due to its proven validity and reliability, ease of completion and repeated use in clinical studies.

The Montreal Instrument for Cat Arthritis Testing – Veterinarian (MI-CAT(V)) is the only CMI to date that can be completed by veterinary surgeons in conjunction with the physical examination. In the preliminary study which was conducted in a laboratory colony of cats, only the items assessing gait and body posture were promising, but no scale items distinguished healthy cats from cats suffering from DJD in the follow up evaluation (Klinck et al., 2015). The revised MI-CAT(V), also tested on laboratory cats, was able to detect naturally occurring DJD, but not treatment effects (Klinck et al., 2018b). Consequently, further studies are needed to confirm the instrument's performance in client-owned cats.

1.4.1.2 Quality of Life

In human medicine, the importance of patient-reported outcomes is widely recognised, as they provide important information relating to health outcome endpoint data, such as clinical signs, quality of life (QoL) and health related QoL (HRQoL) as well as treatment adherence (Arpinelli and Bamfi, 2006). The World Health Organisation defines QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns (World Health Organisation, 1995). Since QoL is a broad, complex, and multidimensional concept, HRQoL attempts to focus on the QoL aspects which are affected by disease and can possibly be modified by treatment. In animals, HRQoL is also a multidimensional concept, including both physical and non-physical factors, such as comfort/discomfort and feelings, respectively (Mullan, 2015). Assessment of QoL in animals has similar challenges to chronic pain assessment; it relies on owners identifying issues that are affecting their animals' QoL since animals are unable to self-report. Measurement of HRQoL can be used to identify or highlight QoL concerns that had not been previously perceived by the owner or to monitor changes in QoL over time in an

animal suffering from a chronic disease (Yeates and Main, 2009). Consequently, it can be a valuable tool for veterinary surgeons as it can help influence treatment decisions.

1.4.1.2.1 Assessment Using Quality of Life Instruments

There are numerous instruments which attempt to quantify QoL and HRQoL in veterinary medicine. Some are disease-specific, focusing on an individual condition, whilst others are generic, designed to be used more broadly. Disease-specific instruments can be more sensitive in recognising clinical changes, however generic instruments may be preferred when an animal is suffering from more than one disease, such as in the case of older cats.

A plethora of disease-specific HRQoL instruments have been developed for cats, focusing on cardiac disease (Freeman et al., 2012, Reynolds et al., 2010, Rush et al., 2015), diabetes mellitus (Niessen et al., 2010), hyperthyroidism (Boland et al., 2014), feline infectious peritonitis (Fischer et al., 2011), skin disease (Noli, 2019, Noli et al., 2016), as well as neoplasia and use of chemotherapy (Lynch et al., 2011, Thornton et al., 2018, Tzannes et al., 2008, Vols et al., 2017). With regards to DJD-associated pain, an initial design of a questionnaire to assess DJD-associated pain and QoL in cats (Benito et al., 2012, Zamprogno et al., 2010) was followed by the development of the FMPI CMI (Benito et al., 2013a, Benito et al., 2013b, Gruen et al., 2015, Zamprogno et al., 2010).

Four generic HRQoL instruments have been published in cats. The first psychometric generic HRQoL to be developed and validated in cats was the CatQoL which contains 16 items (Bijsmans et al., 2016). In the second part of this study, the CatQoL was also used to compare the HRQoL of healthy young cats, healthy older cats, and cats with chronic kidney disease (CKD). The Cat HEalth and Wellbeing (CHEW) Questionnaire contains 33 items and was shown to have good validity as well as internal and test-retest reliability (Freeman et al., 2016). Nevertheless, as all but eight out of 1303 cats were considered perfectly healthy by their owners, the authors suggested that further research is needed to verify its usefulness in a non-healthy cat population. Another

HRQoL instrument containing 16 items was validated and was shown to have good reliability, internal consistency and test-retest reliability in healthy cats (Tatlock et al., 2017). The VetMetrica instrument was the most recent and first web-based generic HRQoL instrument to be developed (Noble et al., 2019), containing 20 items that are allocated in three domains (vitality, comfort and emotional wellbeing [EWB]). Following qualitative analysis of interview data, content validity index scores for relevance and clarity which had been assigned to each item were used to evaluate the content validity of included items, with the prototype VetMetrica instrument containing 39 items. After the first field test, the remaining 20 items were interpreted as part of the vitality, comfort, and EWB domains. Using these data, factor analysis was conducted by Noble and others (2019), with the model adopted accounting for 72% of the variability in the owner response data, confirming construct validity. A scoring algorithm was also developed as some items loaded to more than one domain. Following the second field test which compared sick versus healthy cats, linear discriminant analysis (LDA) showed that the instrument was able to correctly classify 89% of sick cats and 71% of healthy cats, whereas test-retest reliability was moderate for the vitality domain and good for the comfort and EWB domains.

In the researcher's opinion, VetMetrica is currently the best suited generic HRQoL available for assessing QoL in cats with DJD, with or without comorbidities, for several reasons. First, VetMetrica was used in healthy cats as well as in cats with at least one chronic disease, with DJD reported in 56% and 57% of cats in the first and second field test, respectively. Although CatQoL was able to differentiate between healthy cats and cats with CKD, its validity in cats with other diseases has not yet been established. Secondly, veterinary surgeons verified the health status of all cats in the VetMetrica study. Given that approximately 30% of cats considered healthy by the owners were found to be unhealthy by the veterinary surgeons, owner judgement may be unreliable (Noble et al., 2019). Consequently, this might be an issue for all the other instruments where recruited cats were considered healthy based on their owners' perception, with the exception of cats with CKD in CatQoL where the diagnosis was made by a veterinary surgeon. Finally, the VetMetrica instrument is web-based and thus allows automatic data capture, preventing owners from changing their answers to previous questions.

1.4.2 The Placebo Effect in Feline Degenerative Joint Disease

There are three types of placebo effects. The term "placebo effect" is generally used to describe the placebo effect on the patients themselves. This describes the beneficial response of a patient to an inert treatment which is the result of their psychological state as well as the context with which it is administered, rather than the treatment itself (Benedetti, 2013). The caregiver placebo effect refers to effects that can improve the ratings of the subjective assessment provided by caregivers or clinicians, but not objective measures. In turn, the subjective assessment and behaviour of caregivers can affect the patients themselves, further enhancing the placebo effect in a phenomenon termed the placebo-by-proxy effect; this, however, can also affect objective measures (Kossowsky and Kaptchuk, 2015).

A recent study discovered a profound caregiver placebo effect in cats with DJD participating in clinical trials, with 50% to 70% of placebo-receiving cats showing clinical improvement based on the results of both general and specific CMIs (Gruen et al., 2017b). In this study, suggested causes for the caregiver placebo effect included the better care effect, where owner assessed ratings are improved as a result of more follow-ups, as well as the owner's wish for the trial to work and the desire to please the investigator. Although a placebo-by-proxy effect has not been established in cats, the authors suggested theories on how it could impact on the results of both subjective and objective outcome measures in clinical trials (Gruen et al., 2017b). It was proposed that owners may pay more attention and interact more frequently with their cats, thereby increasing their cat's activity levels and improving their own subjective assessments, or that their own positive disposition may result in the cat feeling more positively, resulting in decreased pain levels and improved mobility.

1.4.3 Objective Outcome Measures of Chronic Pain

1.4.3.1 Gait Analysis

Kinetic gait analysis is a technique used to objectively describe locomotion and the forces produced during the gait cycle in order to study musculoskeletal disease. Kinetic gait analysis in cats requires ground reaction force measurement which has been undertaken using force plates and pressure-sensitive walkways (PSW).

A number of studies have used force plates for gait assessment in healthy cats (Corbee et al., 2014, Lavoie et al., 1995), in experimental models of CCL transection (Leumann et al., 2019, Suter et al., 1998), and in cats undergoing total hip replacement (Kalis et al., 2012). Kinetic gait analysis using PSW has been investigated more extensively, with studies to date evaluating its use in healthy cats (Corbee et al., 2014, Lascelles et al., 2007b, Schnabl-Feichter et al., 2017, Stadig and Bergh, 2015, Verdugo et al., 2013), cats undergoing onychectomy (Robinson et al., 2007, Romans et al., 2004), and cats with DJD (Carroll et al., 2011, Guillot et al., 2012, Guillot et al., 2013, Monteiro et al., 2016, Moreau et al., 2013). One limitation in using force plates in cats is the fact that they are usually difficult to direct onto the force plate and are not accustomed to a walking on a lead. Moreover, force plates cannot assess all limbs simultaneously or during several step cycles which can be an issue in cats with DJD given the high prevalence of bilateral disease. The most commonly calculated parameters using force plates and PSW are Peak Vertical Force and Vertical Impulse. Force plates can additionally assess craniocaudal and mediolateral forces, however vertical force is considered the component of greatest magnitude and lowest variability (Schnabl and Bockstahler, 2015).

In summary, ground reaction forces can be used to objectively detect gait changes in healthy cats and, more importantly, in cats with DJD, also serving as an outcome measure in evaluating treatment efficacy (Moreau et al., 2014, Schnabl and Bockstahler, 2015).

1.4.3.2 Accelerometry

Activity monitors such as accelerometers are monitoring devices that have been used in humans, cats, dogs, and other species as a surrogate measure of spontaneous activity, but also to assist with the assessment of other health-related aspects. These devices measure changes that are generated proportionally to the intensity and duration of change in acceleration by using a piezoelectric sensor, then convert them into counts for the chosen measurement period (John and Freedson, 2012). Accelerometers are worn on the animal's collar or harness and are classified as uniaxial, biaxial, triaxial or omnidirectional based on the number of axes used to measure acceleration. Some accelerometers provide real-time data, whilst others need to be removed from the animal in order to export and analyse that data. Accelerometry is a valid objective outcome measure of DJD-related chronic pain in companion animal veterinary medicine (Brown et al., 2010, Lascelles et al., 2008a), enabling the non-invasive assessment of an animal's daily activity within the home environment, away from the stress of the clinic. There are multiple devices marketed to researchers, veterinary surgeons, and the general public, but few are supported by scientific studies (Appendix B).

Actical (Hansen et al., 2007) and Actigraph GT3-X (Yam et al., 2011) were the first accelerometers validated as a measure of activity and distance moved in dogs. Actical was also shown to be a valid outcome assessment tool for evaluating treatment response in dogs with DJD (Brown et al., 2010). Four more devices have been compared against Actical since then. There was a strong correlation between the activity counts of Actical and Whistle (Yashari et al., 2015), Heyrex (Mejia et al., 2019) and Actrigraph wGT3X+ (Belda et al., 2018), whereas a moderate correlation was observed between Actical and PetPace (Belda et al., 2018).

Actical is the only accelerometer validated in cats not only as a measure of activity and distance moved in healthy cats and in cats with DJD (Lascelles et al., 2007c, Lascelles et al., 2008a), but also as a modality to differentiate between cats with DJD and disease-free cats (Guillot et al., 2012). It has therefore been used in a plethora of studies investigating activity levels as well as the treatment effect of different therapeutic interventions in cats with DJD (Gruen et al., 2017a, Gruen et al., 2014, Gruen et al., 2016, Guedes et al., 2018b, Guillot et al., 2013, Lascelles et al., 2010a). ActiWatch-Mini has been used in two studies investigating the

treatment effect of meloxicam and tramadol in cats with DJD (Monteiro et al., 2016, Monteiro et al., 2017), however it has not been validated as a measure of activity and distance moved in cats or compared against Actical. To the researcher's knowledge, no studies have been conducted on the use of any other accelerometers for the evaluation of activity levels in cats.

1.4.3.3 Goniometry

Goniometric joint measurements have been shown to be repeatable and valid in orthopaedically normal cats (Jaeger et al., 2007). The sole study evaluating goniometry in cats with DJD demonstrated that increased range of motion (ROM) measurements were associated with decreased odds of radiographic DJD being present, thereby suggesting that it may be useful in ruling out the presence of DJD (Lascelles et al., 2012).

1.4.3.4 Quantitative Sensory Testing

Quantitative sensory testing (QST) measures mechanical and thermal sensory thresholds to assess somatosensory abnormalities such as hyperalgesia, allodynia and enhanced temporal summation which occur as a result of peripheral and central sensitisation (Adrian et al., 2017). Different devices such as the von Frey anaesthesiometer have been used to assess QST in healthy cats (Addison and Clements, 2017, Machin et al., 2019). Two studies demonstrated that QST was able to successfully differentiate between cats suffering from DJD-associated pain, cats suffering from pain not associated with DJD and non-painful cats (Guillot et al., 2013, Guillot et al., 2014), suggesting that QST may be a valuable diagnostic tool in the clinical setting.

1.4.3.5 Biological Markers

Biological markers, or biomarkers, are defined as characteristics that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a

therapeutic intervention (Biomarkers Definitions Working, 2001). Biochemical and genetic markers have been investigated in addition to physical and imaging DJD markers. In human medicine, cytokines and chemokines such as tumour necrosis factor alpha (TNF-α) and interleukins (IL-1β, IL-6) have been associated with DJD-related structural joint damage, inflammation and pain (Imamura et al., 2014, Schaible, 2012). A study in cats with DJD demonstrated higher serum concentrations of IL-4 and IL-8 in cats with higher radiographic DJD scores, and higher concentrations of IL2, IL-8, and TNF-α in cats with higher orthopaedic exam pain scores (Gruen et al., 2017c). Unfortunately, no single cytokine or group of cytokines was able to reliably differentiate between cats with and without DJD-associated pain and, as the samples were not age-matched against control samples, the increase in IL-8 could be the result of increasing age rather than DJD. Interestingly, a study investigating the genetic and proteomic profiles of cats with DJD suggested that the differentially expressed genes in cats with DJD were related to the disease itself as well as aging (Gao et al., 2013). Leptin, a cytokine produced by adipose tissue, has also been implicated in the development of DJD in humans (Yan et al., 2018) and, possibly, dogs (Kleine et al., 2019), but not cats.

1.4.3.6 Other Objective Measures

Other objective measures have been described in literature; however, these may not be feasible in a clinical setting. One study detected brain changes in cats with DJD-related pain using Positron Emission Tomography, confirming the previous belief that central sensitisation occurs in cats with the disease (Guillot et al., 2015a). Another study evaluating coxofemoral joint kinematics using fluoroscopic images suggested that the ROM of the coxofemoral joint could be used as a marker of DJD-associated impairment (Guillot et al., 2015b). The use of thermographic imaging may also be promising in clinical practice according to a study that showed it can discriminate cats that are in pain (Vainionpaa et al., 2013).

1.5 Management of Degenerative Joint Disease

1.5.1 Advantages of Early Detection

Earlier DJD detection allows veterinary professionals to adopt a multimodal approach to manage the disease, thereby delaying or halting DJD progression and improving the cats' QoL.

1.5.2 Pharmacological Pain Management

Multimodal analgesia involves using a combination of different groups of medications to achieve adequate pain relief and is generally recommended in cats with DJD. By combining drugs that act synergistically and on different levels of the pain pathway, smaller doses of an individual drug are needed, thus reducing the potential for adverse effects.

1.5.2.1 Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesic in veterinary medicine for the alleviation of both acute and chronic pain and have antipyretic, anti-inflammatory and analgesic effects. They act on two cyclooxygenase (COX) isoforms, COX-1 and/or COX-2, or COX and lipoxygenase enzymes, inhibiting the production of prostaglandins from arachidonic acid (Warner and Mitchell, 2004). COX-1 has an important role for many physiological functions, resulting in the production of prostaglandins that regulate gastroprotection, vascular homeostasis and blood clotting, whereas COX-2 is expressed in sites of inflammation and neoplasia (Warner and Mitchell, 2004). Adverse side effects can be seen even with NSAIDs that selectively inhibit COX-2 with a minimal effect on COX-1, and other factors such as tissue concentration, dosing, and individual characteristics (e.g. age) need to be considered.

A plethora of NSAIDs have been studied in cats. The clinical use of acetaminophen is contraindicated, but the administration of appropriate doses of acetylsalicylic acid, carprofen, deracoxib, firocoxib, flunixin, ketoprofen,

meloxicam, piroxicam, robenacoxib, tepoxalin, tolfenamic acid and vedaprofen is generally considered safe (Brondani et al., 2009, Charlton et al., 2013, Lascelles et al., 2007a, Papich, 2008). Carprofen, ketoprofen, meloxicam, robenacoxib, and tolfenamic acid are the only NSAIDs licensed for cats in the United Kingdom. All are licensed for a short course of one to four days, however meloxicam and robenacoxib are also licensed for long-term use. Meloxicam is a selective COX-2 inhibitor and the first NSAID licenced for the management of chronic pain associated with feline DJD. The safety and efficacy of meloxicam in alleviating DJD-associated pain in cats has been evaluated not only subjectively, but also objectively using accelerometers and kinetic gait analysis in double-blinded, placebo controlled randomised studies (Gruen et al., 2014, Gruen et al., 2015, Guillot et al., 2013, Lascelles et al., 2007c). An oral transmucosal spray formulation of meloxicam was shown to be as effective as oral meloxicam in a randomised, blinded study (Monteiro et al., 2016), but has since been withdrawn from the market. Robenacoxib is a "coxib" type of NSAID, demonstrating highly selective and targeted inhibition of COX-2. It is also licensed for the management of chronic pain associated with feline DJD in the UK, with in vitro and in vivo studies attesting to its safety and efficacy (King et al., 2016, Kongara and Chambers, 2018). More recently, the effect of robenacoxib was evaluated objectively in a double-blinded, placebo controlled randomised study using accelerometers (Adrian et al., 2019).

The most common adverse effects associated with long-term NSAID administration in cats receiving meloxicam or robenacoxib are of gastrointestinal nature, primarily vomiting (Gowan et al., 2011, King et al., 2016). With regards to a possible link between chronic NSAID administration and the development of acute kidney injury or chronic kidney disease (CKD), two retrospective studies evaluating the safety of meloxicam administration in older cats with DJD and with or without stable CKD reported no development or progression of CKD when that was administered once daily for six to twelve months (Gowan et al., 2012, Gowan et al., 2011). Nevertheless, the mean dose administered in those studies was lower than the licensed dose in the UK or the doses that have been described as efficacious (Guillot et al., 2013, Gunew et al., 2008, Lascelles et al., 2007c). A prospective, randomised and blinded study evaluating the safety of robenacoxib administration in a similar population of cats with DJD and with or without stable CKD also reported no clinically detected evidence of

development or progression of CKD, respectively; however, the drug was only administered for one month which may not be a sufficient time period to appreciate possible adverse effects on kidney function (King et al., 2016). There are currently no data on the potential adverse effects of chronic NSAID administration on cats with cardiovascular or chronic liver disease in cats (Kongara and Chambers, 2018, Lascelles et al., 2007a, Papich, 2008, Sparkes et al., 2010).

1.5.2.2 Piprants

Grapiprant is part of a new class of drugs, the piprants, which block prostaglandin E2 receptors (Vito et al., 2016). Grapiprant selectively blocks the EP4 receptor of prostaglandin E2, one of the key mediators of inflammation and pain (Woodward et al., 2011) which was also shown to be involved in central sensitisation and chronic pain in humans and animals (Lin et al., 2006, Nakao et al., 2007). The safety and efficacy of grapiprant was evaluated in a prospective, randomised, placebo-controlled study where owners and veterinary surgeons assessed the pain-relieving effect of grapiprant in dogs with DJD (Rausch-Derra et al., 2016). In a more recent study evaluating an induced model of acute arthritis in dogs using force plates (de Salazar Alcala et al., 2019), however, no significant difference was found in lameness reduction between dogs receiving grapiprant and untreated controls. The safety (Rausch-Derra and Rhodes, 2016) and pharmacokinetics (Lebkowska-Wieruszewska et al., 2017) of grapiprant administration have been evaluated in healthy cats, nevertheless there are no studies to date evaluating its efficacy in the treatment of cats with DJD.

1.5.2.3 Centrally Acting Drugs

Centrally acting drugs, such as amantadine, amitriptyline, gabapentin, opioids and tramadol, have been used as adjunctive analgesic drugs to NSAIDs in humans (Dworkin et al., 2007). Some of these have been used in cats with DJD through extrapolation from humans or, more recently, backed by scientific data; nevertheless, none are licensed in the UK for the management of chronic DJD-associated pain.

Amantadine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist that has been used in humans with neuropathic pain (Dworkin et al., 2007) and was demonstrated to attenuate hyperalgesia and allodynia in animal models of neuropathic pain (Robertson and Lascelles, 2010). The pharmacokinetics of experimental amantadine administration in cats have been documented (Siao et al., 2011), however the efficacy of amantadine as an adjunct to a NSAID (meloxicam) has only been evaluated in dogs with DJD (Lascelles et al., 2008b). Consequently, there are currently no clinical data supporting or refuting the use of amantadine in cats.

Gabapentin, a structural analogue of the neurotransmitter γ-aminobutyric acid (GABA), is also commonly used in human medicine for the management of chronic neuropathic pain (Moore et al., 2014). The pharmacokinetics of gabapentin in cats have been documented in two experimental studies (Adrian et al., 2018, Siao et al., 2010). Positive results were seen following long-term use of gabapentin in a case study of three cats exhibiting chronic pain; DJD was confirmed in one of these cats (Lorenz et al., 2013). Gabapentin administration was significantly associated with improvement in owner-identified impaired activities (Guedes et al., 2018b) in a recent blinded, placebo-controlled, randomised crossover-design study in cats with DJD. Nevertheless, a decrease in activity levels was observed using accelerometry; this was attributed to sedation, the most common adverse effect seen with gabapentin administration (Adrian et al., 2018, Guedes et al., 2018b). Opioids such as fentanyl, buprenorphine and tramadol are used for the management of maladaptive and DJD-associated pain in humans (Schaefert et al., 2015), however their role in the management of chronic pain in cats has not been elucidated. Transdermal use of fentanyl, a full μ-agonist, has been evaluated in cats undergoing ovariohysterectomy (Davidson et al., 2004) and onychectomy (Wilson and Pascoe, 2016), but not in cats with DJD-associated chronic pain. The use of buprenorphine, a partial μ-agonist and κ-antagonist, has been evaluated in multiple studies in cats, although they were also mainly focused on acute rather than chronic pain (Steagall et al., 2014). The most reliable routes of buprenorphine administration are the intravenous and the intramuscular route, but neither can be used for the management of chronic pain. Although there are no clinical studies to date, the oral transmucosal route was experimentally demonstrated to be as effective as intravenous administration and lasting up to six hours (Robertson et al., 2005). On the other hand, the rectal

route of administration has recently been reported to be unreliable (Schroers et al., 2018). Subcutaneous administration of a new high-concentration formulation of buprenorphine was also recently shown to be promising and lasting over 24 hours (Doodnaught et al., 2017); unfortunately, this formulation is not presently available in the UK.

Tramadol is a partial μ-agonist and serotonin antagonist whose pharmacokinetics (Pypendop and Ilkiw, 2008) as well as analgesic effect use peri- and intra-operatively (Brondani et al., 2009, Ko et al., 2008) have been documented. In a study where oral tramadol was administered in addition to oral transmucosal meloxicam in cats with DJD, there was a reported decrease in central hypersensitivity, but no other evident positive benefit was demonstrated over meloxicam alone (Monteiro et al., 2016). Two additional prospective, randomised, blinded, controlled, crossover trials evaluated the efficacy of tramadol in feline DJD using subjective as well as objective outcome measures (Guedes et al., 2018a, Monteiro et al., 2017). Although both studies reported a beneficial effect of oral tramadol administration, the activity data analysis was limited in the study by Guedes and others (2018a), and adverse effects (sedation, hypersalivation, gastrointestinal signs) were commonly reported in all three studies. Consequently, the use of tramadol as an adjunctive analgesic drug to meloxicam is not presently supported, and more studies can attest to its efficacy for use in cats with DJD.

1.5.2.4 Anti-Nerve Growth Factor Monoclonal Antibodies

Nerve growth factor (NGF) is a neurotrophic factor critical for the normal development of certain neurons which has been shown to play an important role in nociceptor sensitisation both in acute and chronic pain scenarios in humans, cats and dogs (Enomoto et al., 2019, Schnitzer and Marks, 2015). To this end, species-specific anti-NGF monoclonal antibodies (mAbs) have been manufactured in humans (Schnitzer and Marks, 2015), dogs (Lascelles et al., 2015) and, more recently, cats (Gearing et al., 2016). The study of pharmacokinetics and safety of frunevetmab, the felinised anti-NGF mAb, was followed by a pilot proof of concept study in cats with DJD-related pain and mobility impairment (Gruen et al., 2016). In this study, a

positive treatment effect using subjective and objective measures was seen for six weeks following a single subcutaneous injection and no adverse effects were reported. In addition, this was the first time that owners were able to detect the benefit of a therapeutic intervention over a placebo in a blinded, parallel group design study. Nevertheless, an increased incidence of serious adverse events such as osteonecrosis was seen in human patients concurrently receiving NSAIDs and the humanised monoclonal anti-NGF antibodies, tanezumab and fulranumab (Hochberg, 2015). The potentially deleterious effect of concurrent exposure to NSAIDs and mAbs was also suggested in a study in mice where a significant inhibition of NGF expression was demonstrated following NSAID administration (Park et al., 2019).

1.5.2.5 Stem Cell Therapy

Stem cells can differentiate into other types of cells and have potent immunomodulatory properties, which explains the interest in using them in the management of degenerative diseases such as DJD. One approach is to use autologous adult stem cells, with the three known accessible sources being bone marrow, adipose tissue, and blood. In veterinary medicine, adipose tissue is surgically harvested under general anaesthesia and sent for processing; following this, the stem cells are injected intravenously or into the affected joints. Positive outcomes have been reported in three studies of dogs with DJD (Black et al., 2008, Black et al., 2007, Vilar et al., 2013). To date, there are studies investigating the use of stem cell therapy in cats with kidney disease (Quimby, 2019) and gingivostomatitis (Arzi et al., 2016), but not in cats with DJD.

1.5.3 Structure-Modifying Osteoarthritis Agents and Nutraceuticals

Structure-modifying Osteoarthritis Agents and Nutraceuticals (STMOADs) are drugs with the potential to alter the underlying pathophysiological process of cartilage degradation that occurs in DJD.

The STMOADs pentosan polysulfate (PPS) and polysulfated glycosaminoglycan (PSGAG) have been suggested to stimulate articular cartilage growth and limit cartilage degeneration in dogs, however only a moderate level of comfort exists that these relationships are scientifically valid (Aragon et al., 2007). The safety and efficacy of nutraceuticals such as omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], and eicosatetraenoic acid [ETA]), green lipid mussel (GLM) as well as glucosamine and chondroitin sulfate, either on their own or as a part of a diet, has been evaluated in numerous studies over the past decade in dogs. Unfortunately, it is very hard to evaluate the evidence provided by these studies as they report different therapy durations, sometimes include other active ingredients, and the drugs used are produced by different manufacturers, thereby having different compositions. Consequently, the evidence of nutraceutical efficacy in alleviating DJD-related clinical signs in dogs is poor, with the exception of omega-3 fatty acids (Bhathal et al., 2017, Vandeweerd et al., 2012). With regards to GLM, three studies reported an improvement whilst one study did not; however, since GLM contains ETA, it was suggested that part of its effect was due to that (Vandeweerd et al., 2012). Interestingly, a later study also reported an objectively-assessed beneficial effect of a GLM-enriched diet using objective primary outcomes (Rialland et al., 2012), however the evidence regarding GLM is still controversial. The administration of PCSO-524, a compound rich in omega-3 fatty acids extracted from the New Zealand GLM, was recently reported to have a beneficial effect when administered in addition to carprofen (Kwananocha et al., 2016) and firocoxib (Vijarnsorn et al., 2019) in dogs with DJD.

Unfortunately, there is a paucity for nutraceutical studies in cats with DJD. To the researcher's knowledge, there are no studies investigating the use of either PPS or PSGAG and, although the safety of PCSO-524 was evaluated in clinically-healthy, normal cats (Pusoonthornthum, 2017), no further studies have been published to date. A prospective, blinded, randomised, controlled clinical study evaluating a feline DJD diet rich in EPA, DHA and supplemented with GLM and glucosamine/chondroitin sulphate showed significantly increased activity using both subjective and objective measures in the test-diet group compared to the control-diet group (Lascelles et al., 2010a). Although it cannot be said with certainty that these effects were attributable to increased EPA and DHA levels rather than concomitant additional nutritional modifications, a more recent

randomised, double-blinded, placebo-controlled, crossover-design study supported the beneficial clinical effect of EPA and DHA omega-3 fatty acids based on owner perception (Corbee et al., 2013). Another study comparing the efficacy of meloxicam to a supplement containing glucosamine/chondroitin sulphate demonstrated that cats receiving the supplement appeared to improve during study duration, although that was not statistically significant (Sul et al., 2014). In summary, there is some evidence for the administration of omega-3 fatty acids, but not for any other nutraceuticals, in cats with DJD.

1.5.4 Weight Management

In overweight patients with knee osteoarthritis, a 3.1% weight loss was not able to affect pain or improve function in one study (Jenkinson et al., 2009), however in a more recent study, a 10% – 20% weight loss was successful in improving pain levels, function and HRQoL (Messier et al., 2018). In a study evaluating dogs with hip dysplasia resulting in secondary DJD, an 11% – 18% weight reduction of initial body weight resulted in reduction of the observed clinical lameness (Impellizeri et al., 2000). In a more recent prospective study evaluating exclusively obese dogs with hip and/or elbow osteoarthritis using kinetic gait analysis, a noticeable improvement was noted after only a 6% – 9% reduction in body weight (Marshall et al., 2010). The results from these studies confirm that, in dogs, weight loss is associated with clinical improvement and, likely, pain reduction.

There is a paucity of clinical studies evaluating the effect of weight loss in cats with DJD. In a study evaluating a therapeutic diet for cats with DJD, and after controlling for weight and change in weight, the group fed the test-diet showed increased activity levels whereas the group fed the control-diet showed decreased activity levels (Lascelles et al., 2010a). The authors proposed two theories; either that the cats fed the test-diet felt more comfortable, which resulted in increased activity levels and more weight loss, or that the weight loss itself resulted in more activity in the test-diet group, suggesting that weight loss was more important than pain relief. Although weight loss was not significantly different between groups, Lascelles and others (2010a)

advocated that the weight loss observed in the test-diet group could be a combination of increased activity levels and the test-diet itself which was rich in DHA and EPA. Indeed, diets high in DHA and EPA have been shown to decrease adipose tissue mass and supress the development of obesity in rodents (Madsen et al., 2005). In any case, the relationship between weight loss, activity and pain relief has not been elucidated in cats with DJD.

1.5.5 Environmental and Activity Modulation

Environmental modulation in the context of a cat suffering from DJD refers to adding or modifying one or more factors within its environment in order to improve its physical and psychological welfare that has been affected by the disease (Ellis, 2009, Robertson and Lascelles, 2010). These factors refer to aspects of the cat's environment, and can be organised into five "systems": physical resource, nutritional, elimination, social and behavioural (Herron and Buffington, 2010).

- Physical resource system: Cats need to have unrestricted access to resting areas and vantage points where stressors are minimised and/or where they can feel safe at (Herron and Buffington, 2010). The importance of vertical space cannot be overlooked in a cat with DJD, and therefore adding steps or ramps in the environment for cats that have difficulty jumping will facilitate access to raised beds, window ledges and other surfaces (Ellis, 2009, Lascelles and Robertson, 2010, Robertson and Lascelles, 2010). Cat flaps should also be modified for cats with outdoor access. In addition, cats prefer comfortable resting options such as pillows or fleece beds, and a source of heat plays an important role in their choice of a resting place (Ellis, 2009, Robertson and Lascelles, 2010). Consequently, a range of options and a heat source such as a heat mat can greatly improve the comfort of a cat with DJD.
- Nutrition system: Food and water bowls should also be easily accessible. Moreover, cats are natural predators and their hunting behaviour needs to be encouraged in order to provide them with physical and mental stimulation (Ellis, 2009, Herron and Buffington, 2010). This can be achieved by having

multiple food bowls, hiding the food bowl, and using puzzle toys or food trails (Bennett et al., 2012b, Ellis, 2009).

- Elimination system: At least one easily accessible litterbox should be available to all cats irrespective of their lifestyle (indoor or outdoor). This should be of generous size, and with at least one low side to allow easy access and positioning for a cat with DJD-associated pain (Bennett et al., 2012b, Lascelles and Robertson, 2010).
- Social system: Free-ranging cats have been reported to spend approximately 14% of their time grooming (Panaman, 1981). Cats with DJD-related pain may not groom themselves sufficiently, therefore owners should groom their cats providing they don't find it aversive (Robertson and Lascelles, 2010). Grooming as well as actively interacting with the cat and providing play opportunities will not only strengthen the human-animal bond, but is also believed to release neurotransmitters that help cats cope with DJD-related pain (Bennett et al., 2012b, Ellis, 2009).
- Behavioural system: An enriched indoor environment and active involvement from the owner with regards to providing appropriate outlets for play are essential for normal behaviour display in cats. One of these behaviours is scratching, and different substrates will appeal to each cat. As cats tend to scratch more often when stretching following rest, scratching facilities should be placed in proximity to the resting places of cats with DJD (Bennett et al., 2012b).

Offering cats with DJD a complex three-dimensional environment and opportunities to display their natural behaviours, with or without owner interaction, will provide them with mental stimulation and encourage more movement (Ellis, 2009). This has been shown to help maintain muscle tone and mass as well as minimise DJD-associated pain in other species (Lascelles and Robertson, 2010).

1.5.6 Physical Therapies

In the context of DJD, physical therapy aims to alleviate muscular pain and improve mobility in affected joints by utilising a range of modalities such as manual therapy, exercise therapy as well as electrophysical and thermal treatments (Lindley et al., 2010, Sharp, 2012a). There is good evidence for the use of physical therapy in humans, and several canine studies have shown positive results (Dycus et al., 2017, Marsolais et al., 2002, Monk et al., 2006). Although there are no published studies in cats to date, it has been proposed that the same principles and benefits would apply to cats (Sharp, 2012a). In manual therapy, mobilisations and manipulations are used to reduce pain and improve joint ROM, whereas massage and passive movements help maintain muscle mass and tone as well as alleviate pain (Sharp, 2012a). Therapeutic exercise can be land-based or water-based (hydrotherapy), and electrophysical therapies include laser, ultrasound, neuromuscular electrical simulation, and transcutaneous electrical nerve stimulation. Electrophysical therapies as well as heat and cold therapy in conjunction with manual therapy and therapeutic exercise have been shown to have an anti-inflammatory and analgesic effect in humans and dogs with DJD (Sharp, 2012a, Sharp, 2012b). Although the same effect could possibly be seen in cats, there are no published clinical studies to support this to date.

1.5.7 Surgical Management

Surgical management is undertaken when non-surgical management options do not provide adequate pain relief. Depending on the affected joint, surgical techniques include excision arthroplasty, total joint replacement, arthrodesis and, when no other option can be explored, amputation.

1.5.7.1 Excision Arthroplasty

Femoral head and neck excision arthroplasty (FHNE) is indicated for the management of chronic coxofemoral luxation, coxofemoral DJD, failed total hip replacement (THR), and highly comminuted femoral head, neck, or

acetabular fractures (Harper, 2017) as well as hip dysplasia in cats (Perry, 2016). Case reports to date suggest good to excellent functionality both medium-term and long-term following FHNE, although few cats were suffering from DJD (Berzon et al., 1980, Off and Matis, 2010, Yap et al., 2015). In addition, direct comparison between study outcomes is not without issues given the lack of objective measures and the lack of follow-up and/or postoperative radiographs in some cases.

1.5.7.2 Total Joint Replacement

The indications for THR in cats are similar to those for FHNE (Liska, 2010, Perry, 2016) and it has also been used following failed FHNE procedures (Fitzpatrick et al., 2012, Liska et al., 2010). The majority of published case reports, however, evaluate the outcome in cats that have suffered trauma rather than cats suffering from DJD (Kalis et al., 2012, Liska, 2010, Liska et al., 2009, Marino et al., 2012, Witte et al., 2010). Excellent outcomes are generally reported at least in the short-term following THR in the few studies to date (Fitzpatrick et al., 2012, Liska, 2010, Liska et al., 2009, Liska et al., 2010). There are currently no studies in cats comparing THR and FHNE, however measured peak vertical force and impulse returned after THR (Budsberg et al., 1996), but not after FHNE in dogs (Planté et al., 1997).

To the author's knowledge, there are currently no studies evaluating elbow or stifle replacement in cats.

1.5.7.3 Arthrodesis

Arthrodesis is the surgical fusion of two bones at a functional angle across a joint and is indicated when there is unmanageable joint pain or instability, non-reconstructible articular fractures and sepsis (Pettitt, 2018).

Arthrodesis has mainly been reported in literature following trauma rather than management of painful DJD. Pancarpal arthrodesis is indicated following carpal hyperextension, intra-articular fractures, severe shearing injuries, some peripheral nerve injuries and severe DJD (Basa and Johnson, 2019). Only two and one cats

underwent partial or pancarpal arthrodesis (Calvo et al., 2009, Mathis and Voss, 2015) and pantarsal arthrodesis (Alza Salvatierra et al., 2018, DeCamp et al., 1993, Mathews et al., 1995), respectively, due to painful DJD in published case reports to date. The sole case report on stifle arthrodesis also concerns a cat that suffered trauma (Belch et al., 2012), and there are no published studies on elbow or shoulder arthrodesis in cats.

1.5.8 Complementary Therapies

Complementary and alternative therapies such as acupuncture and herbal medicine have been criticised both in human and veterinary medicine for not being evidence-based and for potentially causing harm (McKenzie, 2012). The analgesic mechanism of acupuncture is not fully understood and the results of clinical studies in dogs with DJD are considered controversial (Kapatkin et al., 2006, McKenzie, 2012, Shmalberg et al., 2019, Silva et al., 2017). A scoping review identified 843 citations of acupuncture use in cats, dogs and horses which included 179 experimental studies and 175 case reports/series; out of these, only 17 were in cats (Rose et al., 2017). Although there are studies investigating the use of acupuncture in cats undergoing ovariohysterectomy (Nascimento et al., 2019, Ribeiro et al., 2017), there are no studies supporting the use of acupuncture for the management of DJD-associated pain in cats to date.

1.6 Thesis Objectives

As discussed, the prevalence of DJD is high in cats of all ages and it is likely that the QoL of cats suffering from DJD is impaired. Moreover, little is known about risk factors predisposing cats to DJD apart from advancing age, and there are multiple obstacles that prevent veterinary surgeons from diagnosing DJD in a timely manner. Elucidating the risk factors predisposing cats to this condition and detecting changes early in the development of DJD is important as these changes may still be reversible and, consequently, a preventative multimodal approach could be adopted to delay or reverse further disease progression, thereby improving the QoL of cats with DJD.

The first overall objective of this thesis was therefore to identify new risk factors associated with the occurrence of feline DJD as well as to evaluate previously investigated risk factors identified in the literature. This would be accomplished by examining prospectively collected data from a large-scale longitudinal cohort study of pet cats ("Bristol Cats"; BC).

The second overall objective of this thesis was to evaluate some of the available tools for diagnosing feline DJD, and to ascertain the effect of early DJD-related pain on the QoL of affected cats. Although we are not yet able to directly measure the subjective and emotional experience of chronic pain in cats, we are able to assess the physical dysfunction resulting from chronic pain. Subjective owner assessment questionnaires, orthopaedic examination, and accelerometers would be used in the BC study cohort to a) identify differences in the activity profiles of cats with early DJD-related changes in owner-reported mobility when compared to cats without owner-reported mobility changes, b) establish whether joint health as evaluated by orthopaedic examination reflected early DJD-related changes in owner-reported mobility, c) investigate changes in the QoL of cats with early DJD-related changes in owner-reported mobility, and d) determine whether accelerometry was able to detect early DJD-related changes in owner-reported mobility.

2. STUDY ONE: RISK FACTORS FOR OWNER-REPORTED SIGNS OF EARLY DEGENERATIVE JOINT DISEASE AT SIX YEARS OF AGE

This study was approved by University of Bristol's Health Sciences Faculty Research Ethics Committee (69041; 04/07/2018) and the Animal Welfare and Ethical Review Body (VIN/18/026; 09/08/2018).

2.1 Aims and Objectives

The specific aim of this study was to utilise data from the BC study cohort relating to husbandry and health in order to not only identify novel risk factors associated with the occurrence of feline DJD, but also to evaluate previously investigated risk factors.

2.2 Hypothesis

We hypothesised that early risk factors in the life of cats would influence the development of owner-reported mobility changes related to DJD later in life.

2.3 Materials and Methods

2.3.1 Study Design

A study was designed to identify risk factors for feline DJD in 6-year-old cats by examining prospective data from a longitudinal cohort study, the BC study.

Briefly, the BC study (http://www.bristol.ac.uk/vet-school/research/projects/cats/) is an ongoing longitudinal study of health, behaviour and environment of client-owned cats where data is being collected prospectively

from owners and veterinary surgeons via the use of questionnaires and the sharing of clinical records (with owner permission), respectively. The BC study has been approved by the Ethics of Human Research Committee and by the Animal Welfare and Ethical Review Body (UIN/13/026). A total of 2203 kittens (aged 8-16 weeks) were registered by their owners between June 2010 – December 2013. Questionnaires are being completed by owners at specific intervals during their cat's life; questionnaires one (Q1) at 2-4 months, two (Q2) at six months, three (Q3) at 12 months, four (Q4) at 18 months, five (Q5) at 2.5 years, six (Q6) at four years, then annually thereafter. These questionnaires include information such as cat and owner demographics, cat behaviour, clinical signs of disease and veterinary treatment. The BC study and published findings to date have been described extensively elsewhere (Murray et al., 2017). During 2014-2015, an additional 241 cats registered on another cohort study (Cat Longitudinal Analysis of Welfare Study [C.L.A.W.S.]) were transferred onto the BC study. The C.L.A.W.S. cats were adopted as kittens from rehoming organisations, mainly Cats Protection, and were recruited between May 2012 – May 2013 (http://www.bristol.ac.uk/vet-school/research/projects/claws/). The cohort was designed to investigate early-life risk factors of feline obesity at two years of age (Rowe et al., 2017), and owners completed a series of five questionnaires until that age, with some questions identical to those used for the BC study. After completing the last C.L.A.W.S. questionnaire at two years of age, owners were offered the opportunity to join the BC study, completing their first BC questionnaire when their cats reached 2.5 years of age. With the addition of the C.L.A.W.S. cohort, the total number of the BC study cohort increased to 2444 cats.

2.3.2 Participants

Participants included the entire BC study cohort of 2444 cats, which comprised of 2203 cats from the original BC study cohort and 421 cats from the C.L.A.W.S cohort.

Cats from the BC study were considered for this study if their owners had completed the BC study questionnaire (Appendix C) which was distributed when their cat turned six years of age (Q8). Twelve mobility-related

questions were selected from Q8 (Section E2) based on changes that were most likely to occur as a result of DJD rather than other disease processes. In these questions, owners were asked to rate their agreement to statements relating to their cat's ability to perform different activities with the options "yes", "maybe", "no" and "not applicable". These questions were used to classify cats as Cases or Controls, and owners additionally needed to have completed at least ten out of twelve questions (~80%), answering "not applicable" in less than 50% of those. "Not applicable" was not given a score and the remaining answers were assigned on an integer scale from 0 to 2, with 0 = "no", 1 = "maybe", and 2 = "yes". The total mobility score (MS) was the sum of scores for each question with a range of 0-24. Control cats were required to have no owner-assessed mobility impairment (MS = 0), whereas cats with owner-assessed mobility impairment (MS > 1) were assigned to the Case group. A MS of 1 corresponded to a "maybe" answer to a single question and was excluded to eliminate uncertain answers to a single aspect of mobility which could also have reflected a different disease process to DJD. Conversely, the score of two and above corresponded to one "yes" answer or two "maybe" answers and it was felt that it could reflect early mobility impairment. Finally, cats were not excluded if they were not healthy or if they were currently receiving any analgesic or anti-inflammatory medications.

A total of 986 owners completed the BC study questionnaire which was distributed when their cat turned six years of age (Q8). Thirty-five cats were excluded either because their owners answered less than ten out of twelve questions (< ~80%) or because more than 50% of these were answered with "not applicable". An additional 152 cats were excluded due to having a MS = 1, leaving 799 cats for analysis.

2.3.3 Data Collection

Data on potential early risk factors were obtained from questionnaires completed between the age of 2-4 months and five years (Q1-Q7 inclusive), whereas data on present husbandry and health were obtained from the questionnaire completed at six years of age (Q8). An example of the questionnaires used in this study can be found in Appendix C.

2.3.4 Explanatory Variables

Participating cats were identified using their unique BC study identification number. Variables suggested in the literature to be early life risk factors associated with the occurrence of DJD were considered as predictors in a logistic regression model and are listed in Table 2.1. Keywords used for free text mining of trauma-related injuries are listed in Appendix D.

Table 2.1: Explanatory Variables Considered for Univariable Analysis of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
Sex	Categorical	"What is the sex of your kitten?"	Q1	Male	Male
				Female	Female
Breed Category	Categorical	"What is the breed of your kitten?"	Q1	DSH	DSH, DLH and their crossbreeds
				DLH	
				Remaining specific breeds	Purebred
Breed Classification (Cephalic Index)	Categorical	"What is the breed of your kitten?"	Q1	British shorthair, Burmilla, Exotic shorthair, Persian, Scottish Fold	Brachycephalic
				Korat, Oriental, Siamese, Somali, Tonkinese	Dolichocephalic
				All other breeds	Mesocephalic
Breed Classification (Body Size)	Categorical	"What is the breed of your kitten?"	Q1	Devon Rex, Oriental, Russian Blue, Singapura	Small/Toy
				Bengal, Birman, British shorthair, Exotic shorthair, Maine Coon, Norwegian Forest, Persian, Ragamuffin, Ragdoll, Siamese, Siberian, Somali	Large/Giant
				All other breeds	Medium
	Categorical		Q2	No	Entire

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
Neuter Status at Six Months of Age		"Has your kitten been neutered (desexed)?"		Yes	Neutered
Neuter Status at Six Years of Age	Categorical	"Is your cat neutered (desexed)?"	Q8	No	Entire
				Yes	Neutered
Outdoor Access	Categorical	"Which of these statements best describes your cat's indoor/outdoor access?"	Q8	Inside only – the cat is not allowed outside	No outdoor access
				Inside only – cat only goes out into enclosed run or on a lead	Outdoor access
				Inside and outside	
				Outside only – cat is not allowed in the house	
BCS (12-month-old)	Categorical	"Please assess the body condition of your cat."	Q3	1	Not overweight
				2	
				3	
				4	Overweight/ Obese
				5	
BCS (18-month-old)	Categorical	As above	Q4	1	Not overweight
				2	
				3	
				4	Overweight/ Obese
				5	
BCS (2.5-year-old)	Categorical	As above	Q5	1	Not overweight
				2	
				3	
				4	Overweight/ Obese
				5	
BCS (4-year-old)	Categorical	As above	Q6	1	Not overweight
				2	
				3	
				4	Overweight / Obese
				5	

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
BCS (5-year-old)	Categorical	As above	Q7	1	Not overweight
				2	
				3	
				4	Overweight/ Obese
				5	
BCS (6-year-old)	Categorical	As above	Q8	1	Not overweight
				2	
				3	
				4	Overweight/ Obese
				5	
CKD Diagnosis	Categorical	"Has a veterinary surgeon diagnosed your cat with CKD?"	Q8	Yes	Yes
				No	No
Dental Health	Categorical	"During the last 12 months, has a veterinary surgeon/nurse commented on the health of your cat's teeth and mouth?"	Q8	Advised that teeth and mouth are in good health	Good
				Advised that cat has some dental/oral disease and that dental treatment (under anaesthetic) may be necessary in the future	Dental disease present
				Advised that that cat has a S&P (under anaesthetic)	
				Advised that cat has dental/oral disease and recommended that dental treatment under anaesthetic (excluding S&P only) was needed	
				No comment on teeth/mouth made	Answers treated as missing data and not analysed
				N/A – has not seen a vet or vet nurse in the past 12 months	

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
Vaccination History	Categorical	"Has your cat visited the veterinary practice in relation to being vaccinated?"	Q2 Q3 Q4 Q5 Q6 Q7 Q8	Yes No	See text for information on final categories
Trauma Incidence	Categorical	"Has your cat been hit by a vehicle since you have owned him/her?"	Q2 Q3 Q4 Q5	Yes Unsure No	See text for information on final categories
	Categorical	"Has your cat had any of the following injuries that you sought veterinary attention for: Dog bite, Cat bite and/or abscess, Lameness / limb problem (including broken or dislocated bone)?" & Free text mining	Q2 Q3 Q4 Q5 Q6 Q7	Yes No	

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
	Categorical	"Has your cat had any of the following injuries which you felt were not serious enough to seek veterinary attention for: Dog bite, Cat bite and/or abscess, Lameness / limb problem?" & Free text mining	Q2 Q3 Q4 Q5 Q6 Q7	Yes	
				No	

Body condition score (BCS); Chronic kidney disease (CKD); Domestic short hair (DSH); Domestic long hair (DLH); Not applicable (N/A); Road traffic accident (RTA); Scale and polish (S&P).

With regards to their breed, cats were organised in two additional categories. The first category was according to the cephalic index, the ratio between the width and length of a cat's skull, with cats grouped as brachycephalic, mesocephalic and dolichocephalic (Farnworth et al., 2018). British short hair, Burmilla, Exotic shorthair, Persian and Scottish Fold cats were considered brachycephalic, and Korat, Oriental, Siamese, Somali and Tonkinese and were considered dolichocephalic. The remaining cat breeds were classified as mesocephalic. The second category was based on average breed body size, with cats classified as small/toy, medium and large/giant (Purina, 2020). Bengal, Birman, British shorthair, Exotic shorthair, Maine Coon, Norwegian Forest, Persian, Ragamuffin, Ragdoll, Siamese, Siberian and Somali cats were classified as large/giant, and Devon Rex, Oriental, Russian Blue, and Singapura were classified as small/toy. The remaining breeds were considered of medium size.

Taking into account the outdoor access of each cat and the level of exercise it permitted, cats were grouped for analysis as having "no outdoor access" ("inside only – the cat is not allowed outside") or having "outdoor

access" ("inside only – cat only goes out into enclosed run or on a lead", "inside/outside", and "outside only – cat is not allowed in the house").

As data were sparse for the lower BCS using the 5-point system (Laflamme, 1997), cats were grouped for further analysis as "overweight/obese" for BCS 4–5, which included both overweight (4) and obese (5) cats, or "not overweight" for BCS 1–3, which included underweight (1–2) cats and cats of ideal weight (3).

Data were also sparse for some dental health categories, and thus these were collapsed for analysis as 0 = "good health" ("advised that teeth and mouth are in good health") or 1 = "dental disease" ("advised that cat has some dental/oral disease and that dental treatment (under anaesthetic) may be necessary in the future", "advised that cat has a S&P (under anaesthetic)", "advised that cat has dental/oral disease and recommended that dental treatment under anaesthetic (excluding a S&P only) was needed"), whilst 2 = "no comment on teeth/mouth made" and "N/A – has not seen a veterinary surgeon/nurse in the past 12 months" were treated as missing data and were not analysed.

The question relating to whether the cat had been vaccinated was categorised as 0 = No and 1 = Yes for each questionnaire. In order to be analysed, answers to these questions were grouped into the following categories according to previous research (Finch et al., 2016): a) Never vaccinated, b) Primary vaccinations only, c) Occasional vaccination (> 2-year interval), d) Frequent or annual vaccination (every 1-2 years), and e) Unknown vaccination status. An unknown vaccination status was given to cats with missing data in > 50% of possible answers with the remaining being negative; these were treated as missing data and were not analysed. As data were sparse for some categories, they were collapsed as follows: 0 = "Never vaccinated / Primary vaccinations only", 1 = "Occasional vaccination", and 2 = "Frequent or annual vaccination", with cats of unknown vaccination status again treated as missing data and not analysed.

The RTA-related question ("Has your cat been hit by a vehicle since you have owned him/her?") was coded as follows: 0 = No ("No"), 1 = Unsure ("Unsure"), 2 = Yes ("Yes – at my current address" and "Yes – at my previous address"). Due to the nature of the positive answer, data prior to any positive answer were examined to ensure

no RTA was counted twice and were then collapsed as 0 = No ("No") and 1 = Yes ("Yes" and "Unsure"). Additional trauma-related information was acquired by free text mining as well as analysing two more questions relating to injuries that received veterinary treatment and injuries that the owners deemed were not serious enough to seek veterinary attention for. All trauma-related information was used to classify trauma as RTA, fall from height, fracture/dislocation, dog or cat bite and abscess, and soft tissue trauma (STT). When the exact nature of lameness was unclear, it was classified as STT. Following this, the researcher obtained advice from an orthopaedic surgeon with regards to categorising trauma further. Answers to questions pertaining to sustained trauma were grouped into the following categories in order of severity from least to most severe: a) STT, b) Dog or cat bites and abscesses, and c) RTAs/Falls from height/Fractures/Dislocations. In addition, only the most severe injury was retained for cats that had sustained more than one type of injury, and only the oldest injury was retained for cats that had sustained the same type of injury multiple times. In the end, all trauma-related data were collapsed for analysis to reflect if trauma had occurred or not (0 = No, 1 = Yes) since data were sparse for some trauma categories. Data from Q8 were not used to collect trauma-related information as it was felt that it would not have caused a chronic inflammatory process such as DJD to develop in such a short time.

The age when the oldest and most severe trauma occurred was also noted based on the questionnaire where it was reported, with possible answers being 6 months, 12 months, 18 months, 2.5 years, 4 years, and 5 years.

Following construction of the final model, a subsequent logistic regression model was formulated to investigate the effect of BCS at six years of age on the initial model. These additional composite variables described the change in BCS between cats aged 6 years and 12 months, 18 months, 2.5 years, 4 years and 5 years, respectively, and had possible outcomes of -2 = lost two BCS units, -1 = lost one BCS unit, 0 = no BCS change, 1 = gained one BCS unit, 2 = gained two BCS units and 3 = gained 3 BCS units (Table 2.2). They were grouped for analysis as 0 = no BCS change, 1 = BCS decrease and 2 = BCS increase due to incomplete information in some categories.

Table 2.2: Additional Explanatory Variables to Investigate the Effect of Body Condition Score at Six Years of Age on the Initial Logistic Regression Model

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
BCS change between 6- and 5-year-old cats	Categorical	"Please assess the body condition of your cat."	Q8	1	See text for information on final categories
				2	
				3	
				4	
				5	
			Q7	1	
				2	
				3	
				4	
				5	
BCS change between 6- and 4-year-old cats	Categorical	"Please assess the body condition of your cat."	Q8	1	See text for information on final categories
				2	
				3	
				4	
				5	
			Q6	1	
				2	
				3	
				4	
				5	
BCS change between 6- and 2.5-year-old cats	Categorical	"Please assess the body condition of your cat."	Q8	1	See text for information on final categories
				2	
				3	
				4	
				5	
			Q5	1	
				2	
				3	
				4	
				5	
BCS change between 6-year- and 18-month-old cats	Categorical	"Please assess the body condition of your cat."	Q8	1	See text for information on final categories
				2	
				3	
				4	

Variable Name	Variable Type	Question(s) used	Questionnaire number	Questionnaire answers	Final categories
				5	
			Q4	1	
				2	
				3	
				4	
				5	
BCS change between 6-year- and 12-month-old cats	Categorical	"Please assess the body condition of your cat."	Q8	1	See text for information on final categories
				2	
				3	
				4	
				5	
			Q3	1	
				2	
				3	
				4	
				5	

Body Condition Score (BCS).

2.3.5 Statistical Analysis

Analyses were performed using SPSS (version 24.0.0.2, IBM Corporation, USA). An alpha value of ≤ 0.05 was set for statistical significance in all analyses, and an exact significance (2-tailed) is reported.

The cat's status reflected the absence (Control = 0) or presence (Case = 1) of owner-reported early DJD-related signs at six years of age and was the outcome variable.

All explanatory variables were of categorical (ordinal or nominal) nature. A correlation matrix was initially constructed in order to test for multicollinearity between all explanatory variables. If two or more explanatory variables were highly correlated (Spearman's $\rho > |0.8|$), only one was taken forward to the univariable models. Univariable analysis was conducted using binomial logistic regression models to examine the association of all potential explanatory variables with the outcome of owner-reported presence of early DJD-related signs at six years of age; only variables with a Wald test $p < 0.2$ were considered for inclusion in the multivariable model. A multivariable model was then constructed to explore and quantify the presence of independent associations between different predictor variables and the odds of a cat having owner-reported early DJD-related signs at six years of age. The multivariable model was built using a backwards elimination method, and removal of variables was undertaken based on minimising the log likelihood-ratio statistic (-2LL). The Hosmer and Lemeshow test (R^2_L) was used to assess the fit of the model whilst Cox-Snell's and Nagelkerke's R2 were used as an approximate effect size measure for the model.

2.4 Results

2.4.1 Participants

At the time of Q8 completion, all 799 included cats were six years of age, 423 (53.1%) were male, and 787 (99.1%) were spayed/castrated (Table 2.3).

Table 2.3: Demographic Data for n = 799 Cats

		N (%) of cats
Sex	Male	423 (53.1%)
	Female	374 (46.9%)
	Total	797 (99.5%)
	Missing	*2 (0.3%)*
Neuter Status at Six Years of Age	Entire	7 (0.9%)
	Neutered	787 (99.1%)
	Total	794 (99.4%)
	Missing	*5 (0.6%)*
Breed Category	DSH, DLH and their crossbreeds	637 (80.3%)
	Purebred	156 (19.7%)
	Total	793 (99.2%)
	Missing	*6 (0.8%)*
Outdoor Access	No – Inside only	92 (11.5%)
	Yes – Only in an enclosed run or on a lead	86 (10.8%)
	Yes – Inside and outside	618 (77.5%)
	Yes – Outside only	1 (0.1%)
	Total	797 (99.7%)
	Missing	*2 (0.3%)*

Domestic shorthair (DSH); Domestic longhair (DLH).

There was missing information concerning the breed of six (0.8%) cats. The majority of the remaining 793 (99.2%) cats (n = 637, 80.3%) were DSH, domestic longhair (DLH) and their crossbreeds (Appendix E). Most cats (n = 553, 69.2%) lived in a single-cat household, whereas 214 (26.8%), 24 (3%), and 8 (1%) cats lived in a household with a total of two, three and four cats, respectively. Two (0.25%) and nine (1.12%) cats were receiving joint supplements or medication on a long-term basis, respectively; six cats were receiving steroids, and three cats were receiving NSAIDs.

2.4.1.1 Breed Classifications

When classified according to their cephalic index, most cats were mesocephalic (n = 713, 89.9%), followed by 52 (6.6%) brachycephalic and 28 (3.5%) dolichocephalic cats (Figure 2.1).

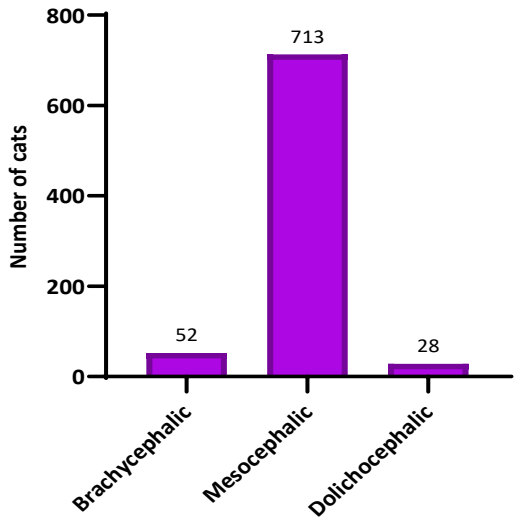

Figure 2.1: Breed Classification according to Cephalic Index for n = 793 Cats

When classified according to their body size, most cats were of medium body size (n = 661, 83.4%), followed by 119 (15%) cats of large/giant size and 13 (1.6%) cats of small/toy size (Figure 2.2).

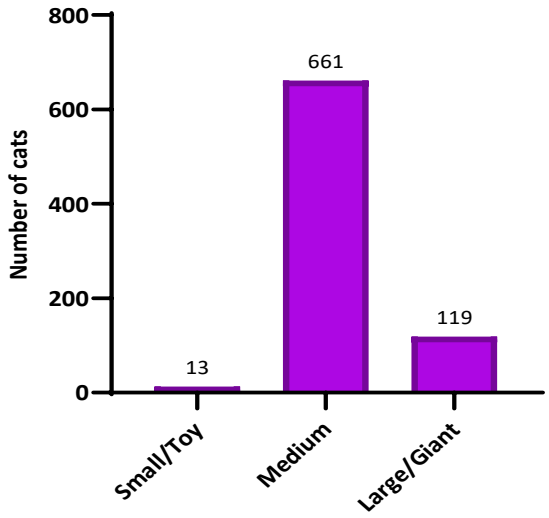

Figure 2.2: Breed Classification according to Body Size for n = 793 Cats

Neither breed classification according to cephalic index nor body size were analysed statistically as two categories in each variable had a very small number of cats.

2.4.1.2 Neuter Status at Six Months of Age

There was missing information in 35 (4.4%) cats. Out of the included 764 (95.6%) cats, 653 (85.5%) cats had been neutered whereas 111 (14.5%) cats remained entire when Q2 was completed at six months of age.

2.4.1.3 Owner-reported Body Condition Score at All Timepoints

Using the 5-point system, owner-reported BCS ranged from 1 to 5 with a median of 3 at all timepoints, whereas interquartile range (IQR) was 3 in cats aged 12 months, 18 months, 2.5 years, 4 years and 5 years, and 3 – 4 in cats aged six years (Table 2.4, Figure 2.3).

Table 2.4: Owner-reported Body Condition Score for n = 799 Cats at All Timepoints

		N (%) of cats
BCS from Q3 (12 months)	1	6 (0.9%)
	2	36 (5.6%)
	3	546 (85.6%)
	4	47 (7.4%)
	5	3 (0.5%)
	Total	638 (79.8%)
	Missing	*161 (20.2%)*
BCS from Q4 (18 months)	1	2 (0.3%)
	2	21 (3.3%)
	3	531 (84.7%)
	4	69 (11.0%)
	5	4 (0.6%)
	Total	627 (78.5%)
	Missing	*172 (21.5%)*
BCS from Q5 (2.5 years)	1	5 (0.7%)
	2	29 (4.1%)
	3	560 (79.8%)
	4	99 (14.1%)
	5	9 (1.3%)
	Total	702 (87.9%)
	Missing	*97 (12.1%)*
BCS from Q6 (4 years)	1	1 (0.2%)
	2	42 (6.5%)
	3	491 (75.7%)
	4	110 (16.9%)
	5	5 (0.8%)
	Total	649 (81.2%)
	Missing	*150 (18.8%)*
BCS from Q7 (5 years)	1	2 (0.3%)
	2	35 (5.5%)
	3	469 (73.7%)
	4	128 (20.1%)
	5	2 (0.3%)
	Total	636 (79.6%)
	Missing	*163 (20.4%)*
BCS from Q8 (6 years)	1	4 (0.5%)
	2	37 (4.8%)
	3	539 (69.5%)
	4	184 (23.7%)
	5	12 (1.5%)
	Total	776 (97.1%)
	Missing	*23 (2.9%)*

Body condition score (BCS).

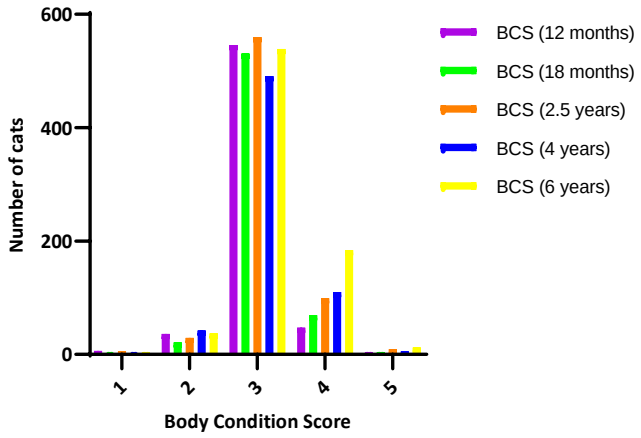

Figure 2.3: Owner-reported Body Condition Score at All Timepoints

Body Condition Score (BCS).

When grouped according to their BCS, the number of overweight/obese cats increased with age, with 50 (7.8%) 12-month-old, 73 (11.6%) 18-month-old, 108 (15.4%) 2.5-year-old, 115 (17.7%) 4-year-old, 130 (20.4%) 5-year-old and 196 (25.3%) 6-year-old cats considered overweight/obese by their owners (Figure 2.4).

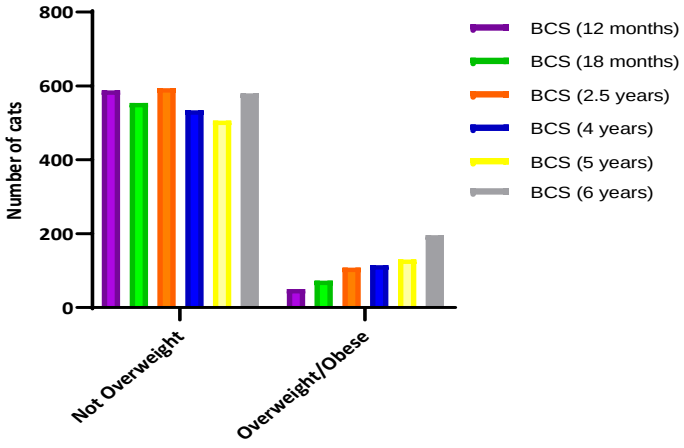

Figure 2.4: Owner-reported Numbers of Not Overweight and Overweight/Obese Cats at All Timepoints

Body Condition Score (BCS).

2.4.1.4 Diagnosis of Chronic Kidney Disease at Six Years of Age

There was missing information on whether cats had been diagnosed with CKD in 285 (35.7%) cats. Out of the included 514 (64.3%) cats, only 4 (0.8%) cats had been diagnosed with CKD and thus it was not possible to analyse this variable statistically.

2.4.1.5 Dental Health at Six Years of Age

There was missing information on the dental health assessment of 19 (2.4%) cats, whilst no comment was made in 143 (17.9%) cats and 134 (16.8%) cats hadn't seen a veterinary surgeon or nurse in 12 months, bringing the number of cats treated as missing data to 296 (37%). Out of the included 503 (63%) cats, good dental health was reported in the majority of cats (n = 376, 74.8%), and dental disease was reported in the remaining 127 (25.2%) cats. Specifically, some dental disease was noted in 104 (20.7%) cats, whereas a scale and polish (S&P) or additional treatment were advised in 12 (2.4%) and 11 (2.2%) cats, respectively (Figure 2.5).

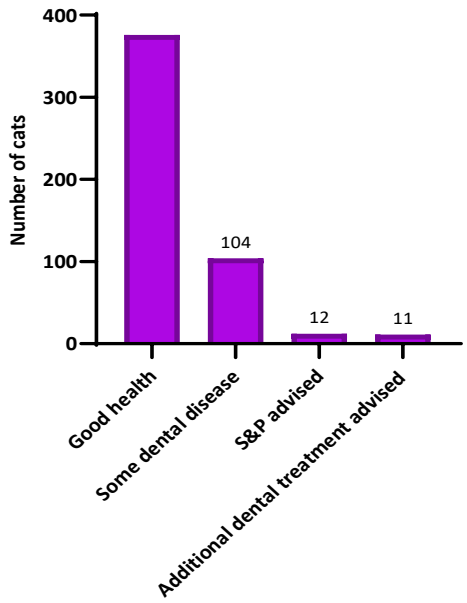

Figure 2.5: Dental Health at Six Years of Age (Assessed by Veterinary Surgeon and Reported by Owners)

Scale and Polish (S&P).

2.4.1.6 Vaccination History at All Timepoints

The incidence of owner-reported vaccinations obtained from each questionnaire is shown in Table 2.5 and Figure 2.6.

Table 2.5: Owner-reported Vaccinations at All Timepoints

		N (%) of cats
Reported Vaccination from Q2 (6 months)	No	22 (3%)
	Yes	712 (96.9%)
	Total	734 (91.9%)
	Missing	*65 (8.1%)*
Reported Vaccination from Q3 (12 months)	No	103 (58.2%)
	Yes	74 (41.8%)
	Total	177 (22.2%)
	Missing	*622 (77.8%)*
Reported Vaccination from Q4 (18 months)	No	324 (42.5%)
	Yes	438 (57.5%)
	Total	762 (95.4%)
	Missing	*37 (4.6%)*
Reported Vaccination from Q5 (2.5 years)	No	290 (39.7%)
	Yes	441 (60.3%)
	Total	731 (91.5%)
	Missing	*68 (8.5%)*
Reported Vaccination from Q6 (4 years)	No	0 (0.0%)
	Yes	520 (100.0%)
	Total	520 (65.1%)
	Missing	*279 (34.9%)*
Reported Vaccination from Q7 (5 years)	No	191 (28.9%)
	Yes	469 (71.1%)
	Total	660 (100.0%)
	Missing	139 (17.4%)
Reported Vaccination from Q8 (6 years)	No	0 (0.0%)
	Yes	446 (100.0%)
	Total	446 (55.8%)
	Missing	*353 (44.2%)*

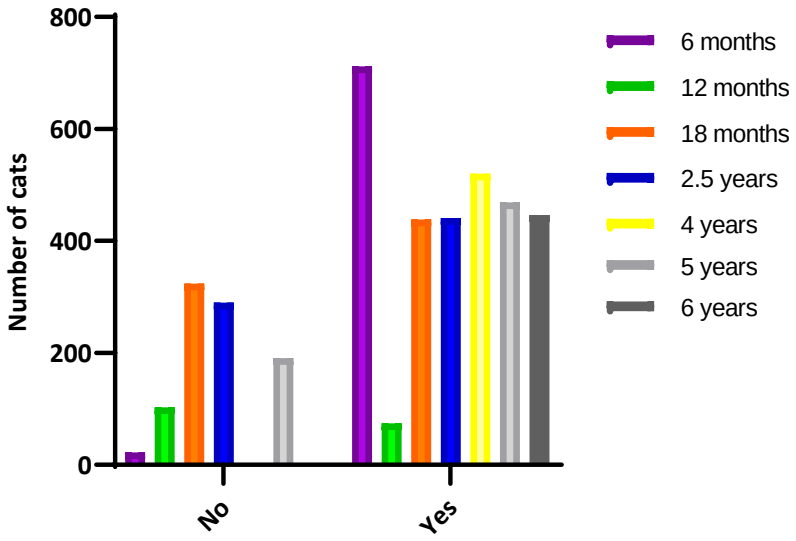

Figure 2.6: Owner-reported Vaccinations at All Timepoints

When grouped according to how frequently vaccinations had been administered, it was possible to determine the vaccination history of all but 16 (2%) cats. Of the remaining 783 (98%) cats, most had been occasionally vaccinated in intervals longer than two years (n = 337, 48.1%), followed by frequent or annual vaccination (n = 308, 39.3%). Primary vaccinations only had been given in 85 (10.9%) cats, whilst 13 (1.7%) cats had never been vaccinated.

2.4.1.7 Trauma Incidence at All Timepoints

The RTA-related question asked the owners if their cat was involved or was suspected to have been involved in an RTA at their current or at their past address, and thus 15 duplicate positive answers were removed. The incidence of owner-reported RTAs until the age of 2.5 years is listed in Table 2.6.

Table 2.6: Incidence of Owner-reported Road Traffic Accidents Until the Age of 2.5 Years

		N (%) of cats
Road Traffic Accidents from Q2 (6 months)	Yes	2 (0.5%)
	Suspected	0 (0.0%)
	No	432 (99.5%)
	Total	434 (54.3%)
	Missing	365 (45.7%)
Road Traffic Accidents from Q3 (12 months)	Yes	9 (1.9%)
	Suspected	1 (0.2%)
	No	471 (97.9%)
	Total	481 (60.2%)
	Missing	318 (39.8%)
Road Traffic Accidents from Q4 (18 months)	Yes	8 (1.7%)
	Suspected	5 (1.1%)
	No	462 (97.3%)
	Total	475 (59.4%)
	Missing	324 (40.6%)
Road Traffic Accidents from Q5 (2.5 years)	Yes	18 (3.9%)
	Suspected	4 (0.9%)
	No	437 (95.2%)
	Total	459 (57.4%)
	Missing	340 (42.6%)

Additional trauma-related data was mined from Q6 (four years) and Q7 (five years), and the incidence of different types of trauma until the age of six years is shown in Table 2.7. A small number of cats had suffered serious injuries such as an RTA (n = 32, 4%), a fracture/dislocation (n = 11, 1.4%) or a fall from a height (n = 7, 0.9%). Dog bites were also rare (n = 8, 1%). Cat bites and/or abscesses were the most commonly reported injury (n = 107, 13.4%), followed by STT (n = 62, 7.8%).

Table 2.7: Owner-reported Incidence of Different Types of Trauma Until the Age of Six Years

		N (%) of cats
Road Traffic Accident	No	767 (96.0%)
	Once	32 (4.0%)
Fracture/Dislocation	No	788 (98.6%)
	Once	11 (1.4%)
Fall from Height	No	792 (99.1%)
	Once	7 (0.9%)
Cat Bite and/or Abscess	No	692 (86.6%)
	Once	89 (11.1%)
	Twice	16 (2.0%)
	Three times	2 (0.3%)
Dog Bite	No	791 (99.0%)
	Once	8 (1.0%)
Soft Tissue Trauma	No	737 (92.2%)
	Once	54 (6.8%)
	Twice	8 (1.0%)

Following retention of only the oldest and most severe injury for each cat, trauma was reported in 206 (25.8%) cats (Figure 2.7) and, when grouped according to their severity, over half (n = 110, 53.4%) were dog/cat bites and/or abscesses, followed by 50 (24.3%) RTAs, falls, fractures/dislocations, and 46 (22.3%) STTs.

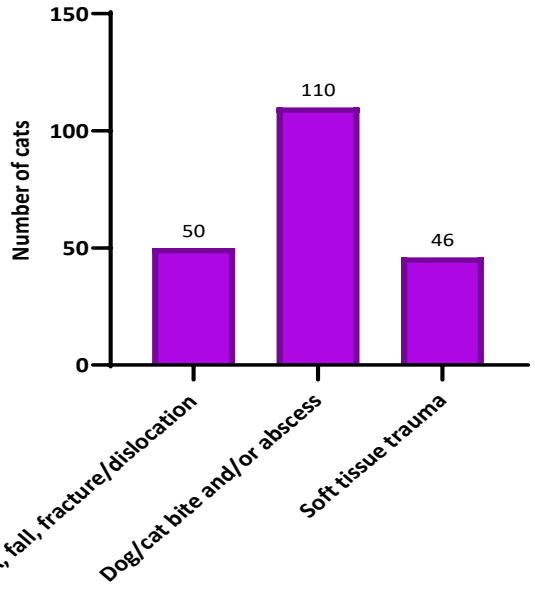

Figure 2.7: Owner-reported Incidence of Trauma According to Severity

For the 206 cats that suffered trauma, this occurred in most cats at the age of 2.5 (n = 64, 31.1%) or 4 (n = 49, 23.8%) years followed by the age of 12 months (n = 27, 13.1%), whereas for 22 cats (10.7%) trauma occurred at the age of 6 months, 18 months, or 5 years.

2.4.2 Logistic Regression Analysis

2.4.2.1 Outcome Variable

Mobility score ranged from 0 to 15 (Figure 2.8) with a median of 0 (IQR = 0 – 2). All 561 Control cats had a MS of 0 and the 238 Case cats had a median MS of 2 (IQR = 2 – 4).

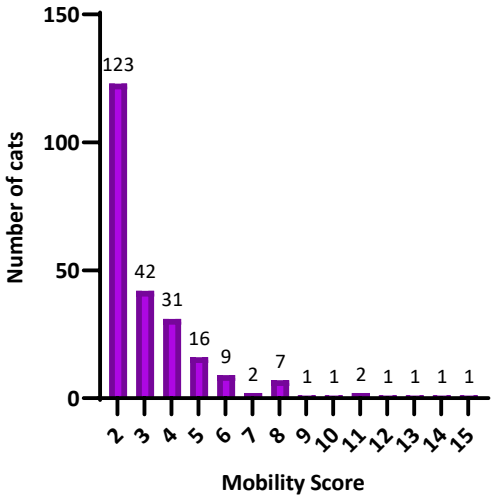

Figure 2.8: Owner-reported Mobility Score for n = 238 Case Cats

2.4.2.2 Explanatory Variables

Where original explanatory variables had low numbers for some categories, these were combined to form new derived variables (Table 2.1). Two composite variables were additionally created by combining information concerning each cat's vaccination and trauma history, respectively. Only 7 (0.9%) cats were entire and thus this variable was not analysed statistically. Thirteen variables were considered for univariable analysis (Table 2.8).

Table 2.8: List of Explanatory Variables Considered for Univariable Analysis of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

Variable Name	Variable Range	All Cats N (%) of Cats	Cases (MS > 1) N (%) of Cats	Controls (MS = 0) N (%) of Cats
Sex	Male	423 (53.2%)	121 (51.1%)	302 (54.0%)
	Female	372 (46.8%)	117 (49.4%)	257 (46.0%)
	Total	795 (99.5%)	237 (99.6%)	559 (99.6%)
Neuter Status at Six Months of Age	Entire	111 (14.5%)	43 (19.0%)	68 (12.6%)
	Neutered	653 (85.5%)	183 (81.0%)	470 (87.4%)
	Total	764 (95.6%)	226 (95.0%)	538 (95.9%)
Breed Category	DSH, DLH and their crossbreeds	637 (80.3%)	186 (78.5%)	451 (81.1%)
	Purebred	156 (19.7%)	51 (21.5%)	105 (18.9%)
	Total	793 (99.2%)	237 (99.6%)	556 (99.1%)
Outdoor Access	No outdoor access	92 (11.5%)	21 (8.9%)	71 (12.7%)
	Outdoor access	705 (88.5%)	216 (91.1%)	489 (87.3%)
	Total	797 (99.7%)	237 (99.6%)	560 (99.8%)
BCS (6-year-old)	Not Overweight	580 (74.7%)	157 (68.0%)	423 (77.6%)
	Overweight/Obese	196 (25.3%)	74 (32.0%)	122 (22.4%)
	Total	776 (97.1%)	231 (97.1%)	545 (97.1%)
BCS (5-year-old)	Not Overweight	506 (79.6%)	145 (76.7%)	361 (80.8%)
	Overweight/Obese	130 (20.4%)	44 (23.3%)	86 (19.2%)
	Total	636 (79.6%)	189 (79.4%)	447 (79.7%)
BCS (4-year-old)	Not Overweight	534 (82.3%)	148 (77.9%)	386 (84.1%)
	Overweight/Obese	115 (17.7%)	42 (22.1%)	73 (15.9%)
	Total	649 (81.2%)	190 (79.8%)	459 (81.8%)
BCS (2.5-year-old)	Not Overweight	594 (84.6%)	174 (84.1%)	420 (84.8%)
	Overweight/Obese	108 (15.4%)	33 (15.9%)	75 (15.2%)
	Total	702 (87.9%)	207 (87.0%)	495 (88.2%)
BCS (18-month-old)	Not Overweight	554 (88.4%)	172 (86.4%)	382 (89.3%)
	Overweight/Obese	73 (11.6%)	27 (13.6%)	46 (10.7%)
	Total	627 (78.5%)	199 (83.6%)	428 (76.3%)
BCS (12-month-old)	Not Overweight	588 (92.2%)	186 (91.2%)	402 (92.6%)
	Overweight/Obese	50 (7.8%)	18 (8.8%)	32 (7.4%)
	Total	638 (79.8%)	204 (85.7%)	434 (77.4%)
Dental Health	Good health	376 (74.8%)	112 (74.7%)	264 (74.8%)
	Dental disease	127 (25.2%)	38 (25.3%)	89 (25.2%)
	Total	503 (63.0%)	150 (63.0%)	353 (62.9%)
Vaccination History	Never / Primary vaccinations only	98 (12.5%)	34 (14.7%)	64 (11.6%)
	Occasional vaccination	377 (48.1%)	115 (49.6%)	262 (47.5%)
	Frequent or annual vaccination	308 (39.3%)	83 (35.8%)	225 (40.8%)
	Total	783 (98.0%)	232 (97.5%)	551 (98.2%)
Trauma Incidence	None reported	593 (74.2%)	157 (66.0%)	436 (77.7%)
	Reported	206 (25.8%)	81 (34.0%)	125 (22.3%)
	Total	799 (100.0%)	238 (100.0%)	561 (100.0%)

Body Condition Score (BCS); Domestic longhair (DLH); Domestic shorthair (DSH).

2.4.2.3 Univariable Models

Prior to univariable analysis, a Spearman Rank correlation matrix was constructed (Figure 2.9); no significant collinearity (Spearman's ρ > |0.8|) was detected between variables and therefore all were taken forward to univariable analysis.

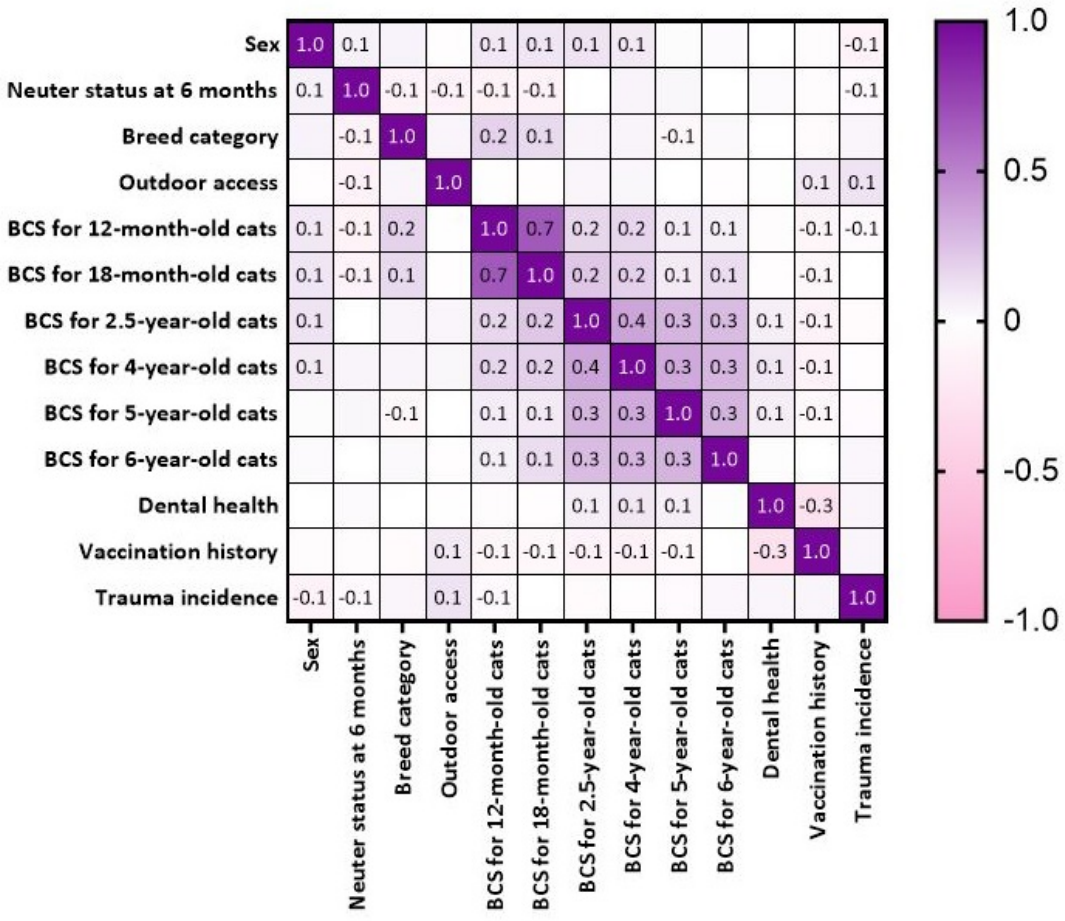

Figure 2.9: Spearman Rank Correlation Matrix of All Explanatory Variables Considered for Univariable Analysis of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

Spearman's ρ values range from 0 to 1, with higher values indicating a stronger relationship between the two examined variables on the x and y axis. The sign of Spearman's ρ indicates the direction of association between the two variables; a positive coefficient suggests that if one variable increases, the other variable tends to do the same, and a negative coefficient suggests that if one variable increases, the other variable tends to decrease. In this case, no two variables were considered highly correlated as all Spearman's ρ values were < |0.8|. Body Condition Score (BCS).

Out of the thirteen variables that were taken forward to univariable analysis, five were significant at $p < 0.2$ and therefore retained for multivariable analysis (Table 2.9). These were: neuter status at six months of age ($p = 0.023$), outdoor access ($p = 0.125$), BCS at four ($p = 0.061$) and six ($p = 0.005$) years of age, and trauma incidence ($p = 0.001$).

Table 2.9: Univariable Logistic Regression Models of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

	N	Categories	B	S.E.	Wald	df	Sig.	OR (CI)	-2LL
Sex	797	Male						Reference	971.167
		Female	0.128	0.155	0.679	1	0.41	1.136 (0.839, 1.54)	
Neuter Status at Six Months of Age	767	Neutered						Reference	922.899
		Entire	0.485	0.213	5.162	1	**0.023***	1.624 (1.069, 2.468)	
Breed Category	793	Purebred						Reference	966.580
		Mixed	-0.164	0.192	0.729	1	0.393	0.849 (0.583, 1.236)	
Outdoor Access	797	No outdoor access						Reference	967.647
		Outdoor access	0.401	0.261	2.353	1	**0.125***	1.493 (0.895, 2.493)	
BCS (12-month-old)	638	Not Overweight						Reference	799.247
		Overweight/Obese	0.195	0.308	0.403	1	0.526	1.216 (0.665, 2.222)	
BCS (18-month-old)	627	Not Overweight						Reference	782.576
		Overweight/Obese	0.265	0.259	1.046	1	0.306	1.304 (0.784, 2.167)	
BCS (2.5-year-old)	702	Not Overweight						Reference	851.395
		Overweight/Obese	0.06	0.228	0.07	1	0.791	1.062 (0.68, 1.659)	
BCS (4-year-old)	649	Not Overweight						Reference	781.345
		Overweight/Obese	0.406	0.216	3.515	1	**0.061***	1.501 (0.982, 2.294)	
BCS (5-year-old)	636	Not Overweight						Reference	772.635
		Overweight/Obese	0.242	0.21	1.33	1	0.249	1.274 (0.844, 1.922)	
BCS (6-year-old)	776	Not Overweight						Reference	937.213
		Overweight/Obese	0.491	0.174	7.924	1	**0.005***	1.634 (1.161, 2.301)	
Dental Health	503	Good health						Reference	612.996
		Dental disease	0.006	0.224	0.001	1	0.977	1.006 (0.649, 1.562)	

	N	Categories	B	S.E.	Wald	df	Sig.	OR (CI)	-2LL
Vaccination History	783	Frequent			2.398	2	0.302	Reference	949.259
		Never / Primary only	0.365	0.248	2.162	1	0.141	1.44 (0.886, 2.342)	
		Occasional	0.174	0.17	1.042	1	0.307	1.19 (0.852, 1.661)	
Trauma Incidence	799	None						Reference	961.581
		Yes	0.588	0.17	11.9	1	**0.001***	1.8 (1.289, 2.513)	

Body Condition Score (BCS); Degrees of Freedom (df); Log likelihood-ratio statistic (-2LL); Odds ratio (OR).
**Variables with p < 0.2 Bootstrap 95% confidence intervals (CI) results are based on 1000 bootstrap samples and are shown in brackets.*

2.4.2.4 Multivariable Model

The initial model included only the intercept, had a -2LL of 897.197, and classified correctly 70.5% of cats. The final model (Table 2.10) included 740 cats and four parameters: neuter status at six months of age, outdoor access, BCS at six years of age, and trauma incidence. In addition, the final model had a -2LL of 866.849, a goodness-of-fit R^2_L = 1.237 (p = 0.872), classified correctly 70.9% of cats and, according to Nagelkerke's R2, had an effect size of 0.057, explaining 5.7% of the variability in the model. Outdoor access was retained in the model as it resulted in a 3.524 change in -2LL and explained an additional 0.8% variability.

Independence of errors was confirmed by evaluating the dispersion parameter, ϕ, which was less than 1. It was not necessary to check the linearity of the logit assumption as none of the explanatory variables were continuous. Additional diagnostics were run to evaluate the presence of influential cases or outliers. None of the studendised and less than 5% of the standardised residuals (n = 6, 0.8%) lay outside ±2, suggesting that the multivariable model included no significant outliers. Although 91 cats (12.3%) in the dataset had leverage values that were more than 2-3 times the average leverage value of 0.0067, Cook's distance and DFBeta values were < 1 for the constant and all predictor variables in all cats, suggesting no influential cases.

Table 2.10: Multivariable Logistic Regression Model of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

		B	S.E.	Wald	df	Sig.	Odds Ratio (95% CI)
Included							
Neuter Status at Six Months of Age	Neutered						Reference
	Entire	0.678	0.226	8.974	1	0.003*	1.97 (1.264, 3.071)
Outdoor Access	No outdoor access						Reference
	Outdoor access	0.513	0.283	3.298	1	0.069	1.671 (0.96, 2.907)
BCS (6-year-old)	Not Overweight						Reference
	Overweight/Obese	0.485	0.184	6.964	1	0.008*	1.624 (1.133, 2.328)
Trauma Incidence	None						Reference
	Yes	0.613	0.179	11.759	1	0.001*	1.846 (1.3, 2.62)
Intercept		-1.745	0.284	37.61	1	0*	0.175
Not Included							
BCS (4-year-old)	Not Overweight						Reference
	Overweight/Obese	-0.023	0.285	0.007	1	0.935	0.977 (0.559, 1.707)

Body Condition Score (BCS); Confidence intervals (CI), Degrees of Freedom (df).
*R^2= 1.237 (Hosmer–Lemeshow), 0.040 (Cox–Snell), 0.057 (Nagelkerke). Model $\chi^2(4) = 30.348$, $p < 0.001$. *$p < 0.05$.*

2.4.2.5 Additional Investigations on the Effect of Body Condition Score at Six Years of Age on the Initial Logistic Regression Model

A subsequent logistic regression model was formulated to investigate the effect of BCS at six years of age on the initial model using additional composite BCS-related variables (Table 2.2).

2.4.2.5.1 Changes in Body Condition Score

Changes in BCS between cats aged 6 years and 12 months, 18 months, 2.5 years, 4 years, and 5 years are shown in Table 2.11 and Figure 2.10.

Table 2.11: Changes in Body Condition Score Between Six-Year-Old Cats and Cats of All Other Ages

	Range	Median	IQR	Total Cats N (%) of Cats	Missing Data N (%) of Cats
BCS Change Between 6- and 5-year-old Cats	-2 to 3	0	0	628 (78.6%)	171 (21.4%)
BCS Change Between 6- and 4-year-old Cats	-2 to 2	0	0	634 (79.3%)	165 (20.7%)
BCS Change Between 6- and 2.5-year-old Cats	-2 to 2	0	0	687 (86.0%)	112 (14%)
BCS Change Between 6-year- and 18-month-old Cats	-2 to 2	0	0	610 (76.3%)	189 (23.7%)
BCS Change Between 6-year- and 12-month-old Cats	-2 to 3	0	0 – 1	623 (78.0%)	176 (22%)

Body condition score (BCS); Interquartile Range (IQR).

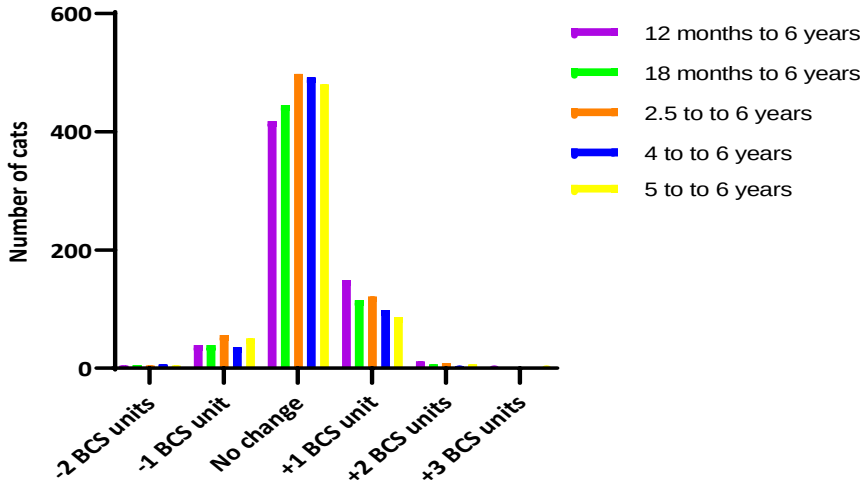

Figure 2.10: Changes in Body Condition Score Between Six-Year-Old Cats and Cats of All Other Ages

Body Condition Score (BCS).

2.4.2.5.1.1 Additional Explanatory Variables

All additional explanatory variables had low numbers for some categories and were combined to form new derived variables (Table 2.12).

Table 2.12: Additional Body Condition Score-related Variables Considered for Univariable Analysis of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

		All Cats N (%) of Cats	Cases (MS > 1) N (%) of Cats	Controls (MS = 0) N (%) of Cats
BCS Change Between 6- and 5-year-old Cats	No change	480 (76.4%)	133 (71.5%)	347 (78.5%)
	Decrease	54 (8.6%)	21 (11.3%)	33 (7.5%)
	Increase	94 (15.0%)	32 (17.2%)	62 (14.0%)
	Total	628 (78.6%)	186 (78.2%)	442 (78.8%)
BCS Change Between 6- and 4-year-old Cats	No change	492 (77.6%)	139 (74.7%)	353 (78.8%)
	Decrease	41 (6.5%)	15 (8.1%)	26 (5.8%)
	Increase	101 (15.9%)	32 (17.2%)	69 (15.4%)
	Total	634 (79.3%)	186 (78.2%)	448 (79.9%)
BCS Change Between 6- and 2.5-year-old Cats	No change	498 (72.5%)	135 (66.2%)	363 (75.2%)
	Decrease	60 (8.7%)	23 (11.3%)	37 (7.7%)
	Increase	129 (18.8%)	46 (22.5%)	83 (17.2%)
	Total	687 (86.0%)	204 (85.7%)	483 (86.1%)
BCS Change Between 6-year- and 18-month-old Cats	No change	445 (73.0%)	130 (67.0%)	315 (75.7%)
	Decrease	44 (7.2%)	18 (9.3%)	26 (6.3%)
	Increase	121 (19.8%)	46 (23.7%)	75 (18.0%)
	Total	610 (76.3%)	194 (81.5%)	416 (74.2%)
BCS Change Between 6-year- and 12-month-old Cats	No change	418 (67.1%)	124 (62.3%)	294 (69.3%)
	Decrease	43 (6.9%)	16 (8.0%)	27 (6.4%)
	Increase	162 (26.0%)	59 (29.6%)	103 (24.3%)
	Total	623 (78.0%)	199 (83.6%)	424 (75.6%)

Body Condition Score (BCS).

2.4.2.5.1.2 Additional Univariable Models

Prior to conducting additional univariable analysis, a Spearman Rank correlation matrix was constructed (Figure 2.11); no significant collinearity (Spearman's $\rho > |0.8|$) was detected between variables and therefore all were taken forward to univariable analysis.

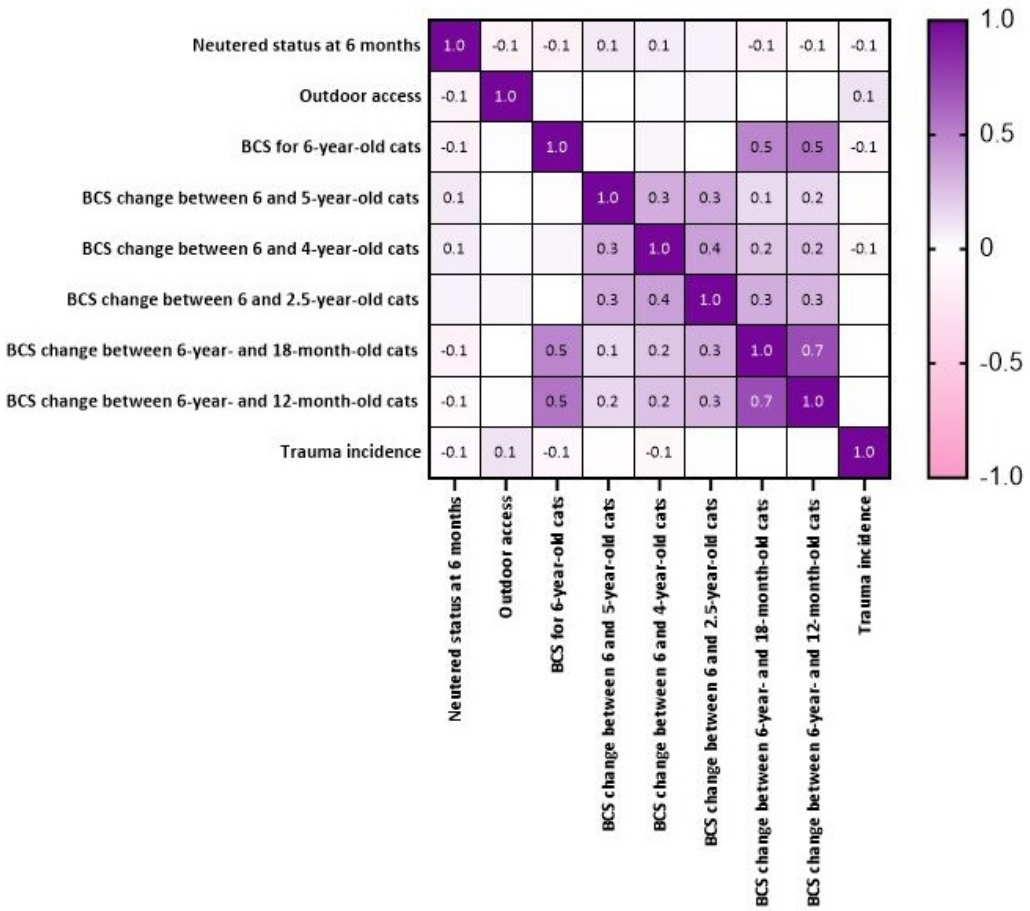

Figure 2.11: Spearman Rank Correlation Matrix of All Confirmed and Additional Explanatory Variables Considered for Univariable Analysis of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

Body Condition Score (BCS).

Out of the five additional explanatory variables, three were significant at $p < 0.2$ and therefore retained for the additional multivariable model (Table 2.13). These were: BCS change between 6- and 5-year-old cats ($p = 0.142$), BCS change between 6- and 2.5-year-old cats ($p = 0.053$), and BCS change between 6-year- and 18-month-old cats ($p = 0.075$).

Table 2.13: Results from Additional Univariable Logistic Regression Models of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

	N	Categories	B	S.E.	Wald	df	Sig.	OR (CI)	-2LL
BCS Change Between 6- and 5-year-old Cats	618	No BCS change			3.911	2	**0.142***	Reference	759.309
		BCS decrease	0.507	0.297	2.91	1	0.088	1.66 (0.927, 2.973)	
		BCS increase	0.298	0.24	1.533	1	0.216	1.347 (0.841, 2.157)	
BCS Change Between 6- and 4-year-old Cats	634	No BCS change			1.576	2	0.455	Reference	765.784
		BCS decrease	0.382	0.339	1.267	1	0.26	1.465 (0.753, 2.849)	
		BCS increase	0.164	0.236	0.48	1	0.488	1.178 (0.741, 1.871)	
BCS Change Between 6- and 2.5-year-old Cats	687	No BCS change			5.889	2	**0.053***	Reference	829.947
		BCS decrease	0.514	0.284	3.271	1	0.07	1.671 (0.958, 2.916)	
		BCS increase	0.399	0.21	3.621	1	0.057	1.49 (0.988, 2.248)	
BCS Change Between 6 and 18-month-old Cats	610	No BCS change			5.171	2	**0.075***	Reference	757.864
		BCS decrease	0.517	0.324	2.552	1	0.11	1.678 (0.889, 3.165)	
		BCS increase	0.396	0.214	3.417	1	0.065	1.486 (0.976, 2.262)	
BCS Change Between 6 and 12-month-old Cats	623	No BCS change			3.03	2	0.22	Reference	777.531
		BCS decrease	0.34	0.333	1.042	1	0.307	1.405 (0.731, 2.699)	
		BCS increase	0.306	0.195	2.458	1	0.117	1.358 (0.926, 1.991)	

Body Condition Score (BCS); Degrees of Freedom (df); Log likelihood-ratio statistic (-2LL); Odds ratio (OR).
**Variables with p < 0.2 Bootstrap 95% confidence intervals (CI) results are based on 1000 bootstrap samples and are shown in brackets.*

2.4.2.5.1.3 Final Multivariable Model

None of the additional explanatory variables improved the previously constructed model; the results of the final backward elimination model are shown in Table 2.14.

Table 2.14: Results from Final Multivariable Regression Model of Risk Factors for Feline Degenerative Joint Disease in Six-year-old Cats

		B	S.E.	Wald	df	Sig.	Odds Ratio (95% CI)
Included							
Neuter Status at Six Months of Age	Neutered						Reference
	Entire	0.678	0.226	8.974	1	0.003*	1.97 (1.264, 3.071)
Outdoor Access	No outdoor access						Reference
	Outdoor access	0.513	0.283	3.298	1	0.069	1.671 (0.96, 2.907)
BCS (6-year-old)	Not Overweight						Reference
	Overweight/Obese	0.485	0.184	6.964	1	0.008*	1.624 (1.133, 2.328)
Trauma Incidence	None						Reference
	Yes	0.613	0.179	11.759	1	0.001*	1.846 (1.3, 2.62)
Intercept		-1.745	0.284	37.61	1	0*	0.175
Not included							
BCS Change Between 6 and 5-year-old Cats	No change			1.275	2	0.529	Reference
	BCS decrease	0.329	0.355	0.86	1	0.354	1.39 (0.693, 2.786)
	BCS increase	-0.184	0.297	0.381	1	0.537	0.832 (0.465, 1.491)
BCS Change Between 6 and 2.5-year-old Cats	No change			0.175	2	0.916	Reference
	BCS decrease	0.062	0.379	0.026	1	0.871	1.064 (0.506, 2.236)
	BCS increase	0.109	0.277	0.156	1	0.693	1.115 (0.648, 1.918)
BCS change between 6 and 18-month-old cats	No change			0.014	2	0.993	Reference
	BCS decrease	-0.002	0.444	0	1	0.997	0.998 (0.418, 2.384)
	BCS increase	-0.037	0.317	0.014	1	0.907	0.964 (0.518, 1.792)

Body Condition Score (BCS); Confidence intervals (CI), Degrees of Freedom (df).

*R^2= 1.237 (Hosmer–Lemeshow), 0.040 (Cox–Snell), 0.057 (Nagelkerke). Model $\chi^2(4) = 30.348$, $p < 0.001$. *$p < 0.05$.*

2.5 Discussion

Previous studies have failed to identify risk factors for feline DJD other than age. Nevertheless, this study identified four risk factors that were associated with owner-reported early DJD-related signs at six years of age (Table 2.10); entire neuter status at six months of age, sustained trauma before the age of six years, outdoor access at six years of age, and overweight/obese status according to owner-assessed BCS at six years of age.

Cats that were entire at six months of age were twice as likely to have owner-reported early DJD-related signs than cats that were neutered before that age. No studies to date have established a relationship between neutering and the incidence of musculoskeletal problems (Howe et al., 2000) or long bone fractures (Spain et al., 2004) which could result in secondary DJD later in life; however, these retrospective cohort studies only had a median follow-up time of approximately three years. This is the first study where the occurrence of feline DJD in relation to neutering has been assessed. Neutering has been shown to result in delayed physeal closure of long bones in cats and dogs of both sexes (Kustritz, 1999). In dogs neutered earlier than six months, the increased incidence of genetically mediated musculoskeletal problems such as HD, CCL and elbow dysplasia, all of which can result in secondary DJD, has been attributed to delayed physeal closure (Howe, 2015). Primary DJD in dogs has also been linked to neutering and specifically post-neutering weight gain (Sanderson, 2012), something which has not been shown in cats. Consequently, the postulated explanations for the effect of neutering in dogs do not appear to apply in cats. On the other hand, the immunosuppressive effect of testosterone during the early stages of development has been recognised in humans and other species of both sexes (Martin, 2000, Nunn et al., 2009). In one study, cats that were neutered before the age of 5.5 months were less likely to suffer from feline asthma and gingivitis compared to cats that were neutered later in life (Spain et al., 2004). The effect of early neutering on the immune system of cats has not been elucidated, and neutering has not been established as a risk factor for the development of chronic inflammatory processes such as feline asthma, gingivitis, CKD and DJD. Nevertheless, the protective effect of neutering before the age of six months demonstrated in this study could be explained by the fact that it resulted in reduced circulating

levels of androgens during that developmental period, thereby decreasing the incidence of owner-reported early DJD-related signs at six years of age.

Cats that had sustained trauma were twice as likely to have owner-reported early DJD-related signs than cats that had not sustained trauma. In humans, trauma is a confirmed risk factor for the development of secondary DJD (Felson et al., 2000), however there is little evidence to support this in dogs (Anderson et al., 2018) or cats (Lascelles, 2010). This is the first study where the occurrence of feline DJD following joint trauma has been evaluated. Trauma occurred in approximately a quarter of this study's cats and was therefore higher than the 12.9% reported for the UK pet cat population (O'Neill et al., 2014). Nevertheless, the study by O'Neil and others (2014) only involved cats that attended primary-care veterinary practices, whilst the present study additionally included injuries that the owners felt were not serious enough to seek veterinary attention. On the other hand, the reported prevalence of RTAs for the UK pet population is 60% (O'Neill et al., 2015), and therefore considerably higher than the prevalence of RTAs in this study (~6%). It should be noted, however, that the present study exclusively involved non-fatal RTAs. Unfortunately, there were not enough cats per trauma category to analyse them separately in this study; nevertheless, this relationship appeared to be driven by the most severe injuries (RTAs, fractures/dislocations, falls from height). Approximately a quarter of sustained trauma in this study comprised of severe injuries which have been shown to result in direct joint trauma; indeed, skeletal fractures/dislocations were reported in 60% and 68.9% of cats that were alive on arrival following RTAs (Rochlitz, 2004) or falls from height (Vnuk et al., 2004), respectively. Cat and dog bites and/or resulting abscesses accounted for approximately half of this study's traumatic injuries and could have contributed to the development of early signs of DJD in two manners. Cat bites can puncture soft tissue deeply and even penetrate joints due to the sharp nature of cats' teeth, whereas dog bites can cause severe STT and fractures as a result of the crush injury delivered by dogs' jaws (Dendle and Looke, 2009). Cat and dog bite wounds also contain a plethora of aerobic and anaerobic bacteria with *Pasteurella* species being the most common isolates (Talan et al., 1999). Consequently, in addition to direct joint trauma, cat and dog bites may lead to secondary DJD by instigating bacterial arthritis either by direct inoculation, if they occur close to joints,

or by haematogenous spread. The remainder of sustained trauma in this study was attributed to STS. It is unlikely that a single STT could have contributed to the development of DJD. Nevertheless, this category may have included other types of more severe trauma that were not witnessed, resulting in owners only reporting the lameness rather than the cause of the lameness.

Cats with outdoor access were twice as likely to have owner-reported early DJD-related signs than indoor only cats. The proportion of cats that had an exclusively indoor lifestyle in this study (~11%) was similar to the previously reported 9.1% for the UK pet cat population (Murray and Gruffydd-Jones, 2012). It should be noted, however, that not all cats in this study would have necessarily had outdoor access for the entirety of their lives. Studies to date have not demonstrated a relationship between outdoor access and feline DJD (Hardie et al., 2002, Lascelles et al., 2010b), however these studies evaluated the presence of radiographic DJD rather than the presence of signs of mobility impairment as reported by owners. Outdoor access has been hypothesised to increase the risk of fighting and accidental injury in cats (Buffington, 2002), thus increasing the risk of developing secondary DJD; nevertheless, there was no multicollinearity between outdoor access and trauma incidence in this study. A possible explanation for this is that cats with outdoor access may be more likely to undergo repetitive microtrauma that goes unnoticed, thereby resulting in owners not reporting any lameness. Repetitive microtrauma has indeed been shown to result in altered biomechanics that lead to DJD in dogs (Marcellin-Little et al., 2007), horses (Magnusson and Ekman, 2001) as well as professional athletes and dancers (Rehmani et al., 2015, Yang et al., 2012).

This study found that overweight/obese cats were approximately twice as likely to have owner-reported early DJD-related signs compared to cats that were not overweight. In humans and dogs, obesity has been established as a cause of abnormal joint loading which alters the mechanical and biochemical properties of articular cartilage, thus initiating the DJD process (Guilak, 2011, Marshall et al., 2009). Interestingly, DJD has also been shown to develop in the non-weight bearing joints of obese patients (Cicuttini et al., 1996), indicating that obesity-related biochemical factors may also be involved in the development of DJD. Circulating levels of leptin reflect body fat mass and have been shown to be increased in overweight cats, dogs and humans (Radin

et al., 2009). In humans, the levels of serum and synovial fluid leptin were demonstrated to be higher in patients with DJD compared to patients without DJD, with the expression of leptin and its receptor being positively correlated with the severity of DJD (Yan et al., 2018). Studies in dogs revealed that the levels of synovial fluid leptin were higher in dogs with secondary DJD due to CCL injury (Schmidli et al., 2018) and in dogs with owner-reported signs of impaired mobility (Kleine et al., 2019), thereby supporting the proinflammatory role of leptin in the development of DJD in dogs. Although there is a paucity of studies investigating the role of mechanical and biochemical factors in the relationship between obesity and feline DJD, it is reasonable that these postulations could also apply to cats, therefore explaining this study's link between obesity and DJD. Additional BCS-derived variables were not able to explain the increased proportion of overweight/obese cats from less than 10% at one year of age to approximately a quarter of cats at six years of age, and future studies are needed to dissect the effect of BCS at six years of age on the development of DJD.

Cohort studies have the ability to assess causality and can thus provide the strongest scientific evidence compared to cross-sectional and case-control studies which are prone to non-response and recall bias, respectively (Song and Chung, 2010). Nonetheless, this study also has potential limitations. The population of the present study was generally similar to what has previously been reported in a large cross-sectional UK study (O'Neill et al., 2015), suggesting that it represented the general owned UK cat population. The only difference was the higher proportion of purebred cats in this study (~20%) than the reported 11%. This is most likely explained by the fact that a pedigree breeder was a more common source of cats for the BC study cohort (Wilson et al., 2017) compared to the UK population (Murray and Gruffydd-Jones, 2012). It should however be noted that the studies by O'Neil (2015) and Murray and Gruffydd-Jones (2012) may be less representative of the general owned UK cat population than the BC study as they only included cats that were registered with or attended primary care veterinary practices. Conversely, both these studies and the BC study may have exclusively included more motivated owners; the former only including owners that registered with or attended a primary care veterinary practice, and the later consisting of owners that had voluntarily participated in a six-year-long study. One of the limitations of this study's design was the fact that it depended on owner-

reported data, possibly introducing reporting bias. This bias could have been mitigated if clinical information pertaining to BCS, vaccination history, dental health and trauma incidence was compared against veterinary records, however that was unfortunately not possible within the study's time frame. With regards to the BCS variable, it is accepted that owners tend to underestimate the BCS of their cats (Cave et al., 2012, Colliard et al., 2009), and indeed a similar attitude has been reported in the BC cohort (Rowe et al., 2017). Consequently, the prevalence of obesity in this study may be an underestimation, which would indicate that the relationship between obesity and the development of early DJD-related signs is stronger than detected by the model. Another limitation relates to the effect of hierarchical clustering on the multivariable model, since approximately a third of this study's cats lived in a multi-cat household. Although this may have limited owner-level variation and introduced bias, it was not possible to construct additional multivariable models within the study's time frame.

2.6 Conclusion

The present study identified four risk factors that were associated with owner-reported early DJD-related signs at six years of age, supporting previous beliefs that obesity, outdoor access and a history of trauma predispose cats to developing DJD and illustrating that neutering appears to decrease that risk.

3. STUDY TWO: ORTHOPAEDIC EXAMINATION, QUALITY OF LIFE ASSESSMENT AND ACTIVITY MONITORING OF CATS WITH OWNER-REPORTED SIGNS OF DEGENERATIVE JOINT DISEASE OVER SIX YEARS OF AGE

This study was approved by University of Bristol's Health Sciences Faculty Research Ethics Committee (69041; 04/07/2018) and the Animal Welfare and Ethical Review Body (VIN/18/026; 09/08/2018).

3.1 Aims and Objectives

The specific aims of this study were to:

- Evaluate two owner assessment questionnaires designed to assess chronic pain in cats with musculoskeletal disease (FMPI) and the QoL of cats (VetMetrica) by comparing cats with and without early DJD-related changes in owner-reported mobility.
- Using orthopaedic examination data, compare the joint health of cats with and without early DJD-related changes in owner-reported mobility.
- Using accelerometry, compare the activity data of cats with and without early DJD-related changes in owner-reported mobility.

3.2 Hypotheses

We hypothesised that owners would be able to recognise early DJD-related pain in their cats, and that DJD-related pain has a significant impact on the QoL of affected cats. We also hypothesised that joint health as evaluated by orthopaedic examination would reflect early DJD-related changes in owner-reported mobility, and that accelerometry would be able to identify these owner-reported mobility changes.

3.3 Materials and Methods

3.3.1 Study Design

A nested case-control study was designed in two groups of individuals, Cases and Controls, to:

1. Identify differences in the activity profiles of cats with early DJD-related changes in owner-reported mobility when compared to cats without owner-reported mobility changes.
2. Establish whether joint health as evaluated by orthopaedic examination reflected early DJD-related changes in owner-reported mobility.
3. Investigate changes in the QoL of cats with early DJD-related changes in owner-reported mobility.
4. Determine whether accelerometry was able to detect early DJD-related changes in owner-reported mobility.

3.3.2 Study Size

It was not possible to estimate the anticipated incidence of early DJD-related changes in owner-reported mobility based on relevant literature to date, as this mainly concerns the radiographical presence of well-established DJD (Clarke and Bennett, 2006, Godfrey, 2005, Lascelles et al., 2010b, Slingerland et al., 2011). Sample size calculation was therefore based on practical considerations with regards to the maximum number of cats that could be visited during the allocated time frame; the aim was to recruit 60 cats, 30 in each group.

3.3.3 Setting

The initial intention was to only include cats from the BC study, and therefore participants of the BC study were approached first. Unfortunately, there were not enough eligible BC study participants within a practical driving distance that could be visited within the allocated time frame and budget, and recruitment was expanded to also include non-BC (nBC) study cats. Recruitment began in July 2018 and January 2019 for BC and nBC study

participants, respectively, and ended in October 2019. Data collection began in December 2018 and March 2019 for BC and nBC study participants, respectively, and ended in November 2019. Eligible participants of the BC study were contacted directly via phone, post, or e-mail (Appendix F). To recruit nBC participants, study advertisements were placed on relevant notice boards throughout the University of Bristol campus, posted to local veterinary practices and e-mailed to students and staff using relevant mailing lists (Appendix F). In addition, a social media page was created (https://www.facebook.com/feline.activity.study), and the study was advertised on a press release (Bristol, 2019), radio (BBC Radio Bristol, 22/05/2019), and television (BBC Points West, 22/05/2019).

3.3.4 Participants

Cats were excluded from the study where performing a clinical examination was not ethical, wearing an activity monitor was not possible, a diagnosis which was likely to influence mobility had been made, or medication which was likely to influence mobility was being administered. Inclusion and exclusion criteria are listed in Table 3.1.

Table 3.1: Inclusion and Exclusion Criteria for Study Recruitment

Inclusion Criteria	Exclusion Criteria
≥ 6 years of age	Being fearful of strangers
Cats with owners willing to habituate them to wearing a breakaway (safety) collar if they were not wearing one already	Unable to acclimatise to wearing a collar or unduly stressed by the process
Cats with owners willing to allow the placement of an activity monitor on their collar for a period of two weeks	Diagnosed with any condition that could influence mobility
Indoor only or with restricted outdoor access	Receiving dietary supplements if initiated < 30 days before the visit and/or not continued during the study

Inclusion Criteria	Exclusion Criteria
Live within a 100-mile radius from Bristol Veterinary School (BS40 5DU)	Receiving anti-inflammatory or analgesic medications
	Inadequate number of questions answered to calculate MS or a MS of 1

Mobility Score (MS).

If the cat was not already wearing a collar, owners were required to be willing to habituate their cat to wearing one for the study period. In these cases, a breakaway (safety) collar along with habituation instructions were provided at least two weeks before the visit took place (Appendix G). Cats that were unable to acclimatise to wearing a collar or were unduly stressed by the process were excluded from the study. Cats were also excluded from the study if they were fearful of strangers and therefore performing an orthopaedic examination would not be ethical. Cats that were receiving anti-inflammatory or analgesic medications for any reason were excluded as their administration could affect their mobility. Due to the cost of the accelerometry devices and the risk of losing them, cats that could leave the owners' garden were excluded from the study. Included cats were required to be indoor only or have restricted outdoor access which included being walked on lead or being allowed in an enclosed area for limited periods of time, with or without owner supervision.

Finally, cats were allocated to the Case or Control group according to their MS. Control cats were required to have no owner-assessed mobility impairment (MS = 0). Cats with owner-assessed mobility impairment (MS > 1) were assigned to the Case group, whilst cats with a MS = 1 were excluded. As in the first study, the score of two and above was chosen to reflect early mobility impairment, whilst the score of one was excluded to avoid false positives.

For BC study cats, the most recently completed BC questionnaire (Appendix C) was used to evaluate their eligibility and calculate MS; this was Q8-Q10 for 6-8-year old cats, respectively. For nBC study cats, an online inclusion questionnaire (Online Surveys) containing the same questions relating to mobility was used to

evaluate their eligibility and calculate MS (Appendix H). The same questions and same method of calculating the MS were used here as in the first study.

Of the 1795 BC study cats that were alive at the start of the recruitment period and of the 282 nBC enquires, 1727 and 177 cats, respectively, did not fulfil the eligibility criteria and were thus excluded from this study (Table 3.2).

Table 3.2: Number of Cats and Associated Reasons for Study Exclusion

Reason for Exclusion	Bristol Cat Participants	Non-Bristol Cat Participants
Cat was < 6 years of age	38	10
Cat lived outside the 100-mile study radius	774	14
Cat had unrestricted outdoor access	237	95
Cat reported to be fearful of strangers	46	21
Cat reported likely to be stressed by collar habituation and/or accelerometer wearing process	149	5
Cat diagnosed with a condition that could influence mobility	33	9
Cat receiving anti-inflammatory and/or analgesic medications	65	10
Inadequate number of questions answered to calculate MS	69	1
Cat had a MS = 1	316	12
Total Number of Excluded Cats	**1727**	**177**

Mobility Score (MS).

It was not possible to contact 30 BC and 22 nBC owners, and 16 BC owners declined to participate in the study. A total of 22 BC and 63 nBC owners agreed to participate in this study, and a unique identification number was assigned to each of the 85 recruited cats. A total of 28 cats were removed from the study before (n = 22) or after (n = 6) data collection began, leaving a total of 57 cats for analysis (Figure 3.1).

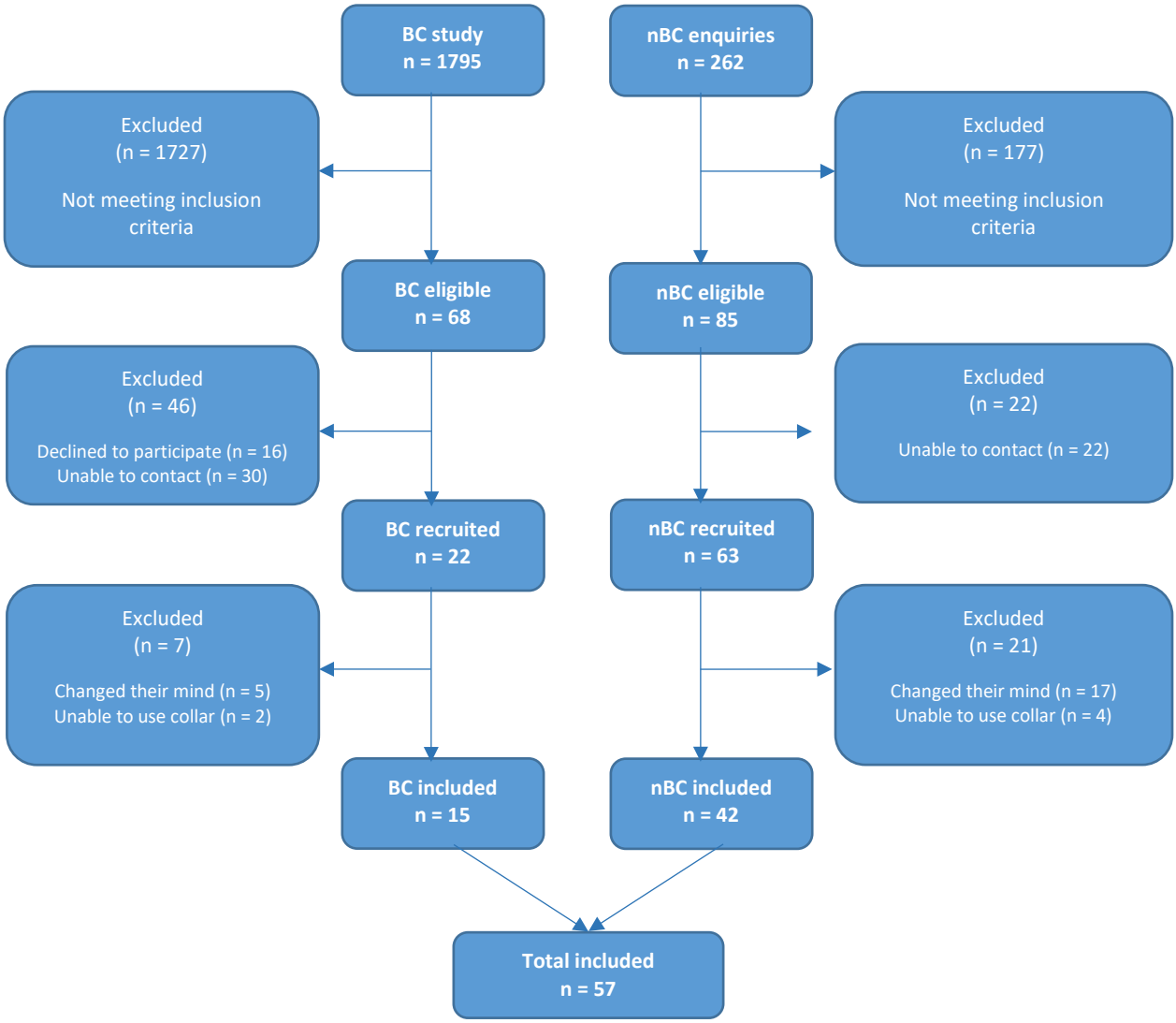

Figure 3.1: Recruitment and Enrolment Flowchart

Bristol Cat (BC) and non-Bristol Cat (nBC) participants.

3.3.5 Data Collection

3.3.5.1 Bias

The researcher was blinded to each cat's MS and other questionnaire results.

3.3.5.2 Pre-visit Measures

The study information sheet and consent form were sent to all eligible owners at least two weeks before the visit took place, and each owner signed an informed consent form prior to participating in the study (Appendices I and J).

Owners of cats meeting the eligibility criteria were additionally asked to complete the FMPI and VetMetrica questionnaires online (Online Surveys) prior to the visit. The FMPI questionnaire (Appendix K) asked owners to rate their cat's ability to perform 17 activities compared to a normal cat on an integer scale from 0 to 4, with 0 = "not at all" and 4 = "normal". The total FMPI score was the sum of scores for each question with a range 0-68. In order to maintain the scale when questions were unanswered or non-applicable, calculation of percent was used for analysis using the following formula:

FMPI% = (sum of answered questions) / (number of questions answered x 4)

To obtain owner responses without passing on their personal information to a third party (VetMetrica), the QoL questionnaire was simulated exactly as it appears on their website on an online survey, not permitting owners to go back and change their answers or skip any questions (Appendix L). The VetMetrica questionnaire (NewMetrica, Glasgow, UK) asked owners to rate how 20 different words described their cat on an integer scale from 0 to 6, with 0 = "not at all" and 6 = "couldn't be more". One final question asked owners to rate the cat's QoL on an integer scale from 0 to 3, with 0 = "very poor" and 3 = "very good". The researcher registered the participating cats on the VetMetrica website using their unique identification number, and owner responses were inputted to the VetMetrica website manually with an appropriate check for accuracy via a

second person. Using the responses to the 20 initial questions, a proprietary algorithm automatically generated scores for the Vitality, Comfort and EWB QoL domains. The final question was not utilised in the algorithm.

A clinical and orthopaedic examination protocol (Appendix M) was developed and piloted by the researcher with advice from an orthopaedic veterinary surgeon.

3.3.5.3 Visit Protocol

Participating cats were visited in their own homes. The duration of each visit was 30 to 60 minutes, and the first 15 to 30 minutes were dedicated to discussing the visit protocol with the owners, allowing the cat to acclimatise to the researcher's presence before any handling took place. A physical and orthopaedic examination was then performed on the cat by the researcher, a veterinary surgeon. This lasted approximately two minutes in most cases. If at any point the cat showed behavioural signs of anxiety or fear, the researcher would pause the examination to allow the cat further time to habituate to their presence before trying again, depending on the individual circumstances and owner consent. If the cat avoided the researcher or showed signs of anxiety at the second attempt, the clinical examination was abandoned.

The BCS was recorded, then each joint comprising the appendicular and axial skeleton was evaluated. The orthopaedic examination would follow the same order for all cats (right foreleg, right hindleg, left foreleg, left hindleg, axial skeleton). Pain responses for each joint were graded using a previously published integer scale (Lascelles et al., 2010b), where 0 = no resentment; 1 = mild withdrawal, mild resistance to manipulation; 2 = moderate withdrawal, body tenses, may orient to site, may vocalise/increase vocalisation; 3 = orients to site, forcible withdrawal from manipulation, may vocalise or hiss or bite; 4 = tries to escape or prevent manipulation, bites or hisses, marked guarding of area. Each appendicular joint was additionally evaluated for the presence of crepitus, thickening and effusion on an integer scale, where 0 = none; 1 = slight – moderate; 2 = severe. Finally, a score was assigned to each cat based on their temperament during the orthopaedic examination, with 0 = neutral attitude, purring, kneading; 1 = resistance to restraint; 2 = resistance to restraint, growling and

hissing; 3 = resistance with biting and scratching, hissing, spitting, and vocalising; and 4 = resistance with biting, scratching, vocalising, spitting, hissing urinating, or defecating (Jaeger et al., 2007). Following this, an activity monitor which was to be worn for a total period of fourteen days was placed upright on the ventral aspect of each cat's collar (Figure 3.2).

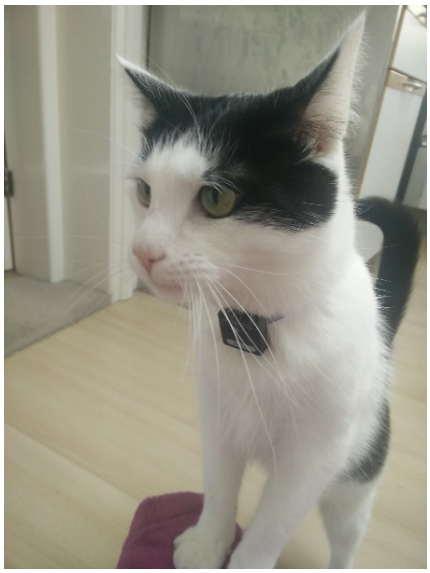

Figure 3.2: Study Participant Wearing the Collar-mounted Activity Monitor

The activity monitor used was Actical® Z (Philips Respironics, Bend, Oregon USA), an omni-directional activity monitor with a titanium frame that measures 29mm x 37mm x 11mm, weighs 16g, and has a piezoelectric sensor mounted to an internal circuit board (Respironics, 2018). The sensor can measure analog voltage changes that are generated proportionally to the intensity and duration of change in acceleration (John and Freedson, 2012). The measurement range of this sensor is between 0.05 and 2G, whilst the measurement bandwidth is between 0.035 to 3.5Hz. The readings are converted into counts of 100 for the chosen measurement period (epoch) when the accelerometer reading goes above 0.02 G (at 1G peak). Actical® Z has a 32Hz sampling rate and can collect data in epoch lengths ranging from one second to one minute, or in raw collection mode. Depending on the set epoch, battery life allows recording from 12 to 301 days. There were

four devices available, all newly purchased and calibrated by the manufacturer at the same time. Epoch length in this study was set to one second, with each daily activity profile composed of 86400 second-by-second measurements. Recording was set to start the following morning (8:00 AM local time) to avoid the confounding effects of the visit and acclimation to wearing the activity monitor. The activity monitor was worn throughout the two-week study period, following which the researcher would visit the cat again to remove the device. Activity data were downloaded using a designated serial port reader (Actireader®) and software (Actical® 3.10); this created a graph containing activity counts per day (Figure 3.3) and imported raw data into an Excel spreadsheet to be used for statistical analysis. Finally, the owners were asked to keep a diary, recording the times when the device and/or the collar fell off and were replaced (Appendix N). Neither the examination findings nor the accelerometer outputs were shared with the owners in any oral or written form.

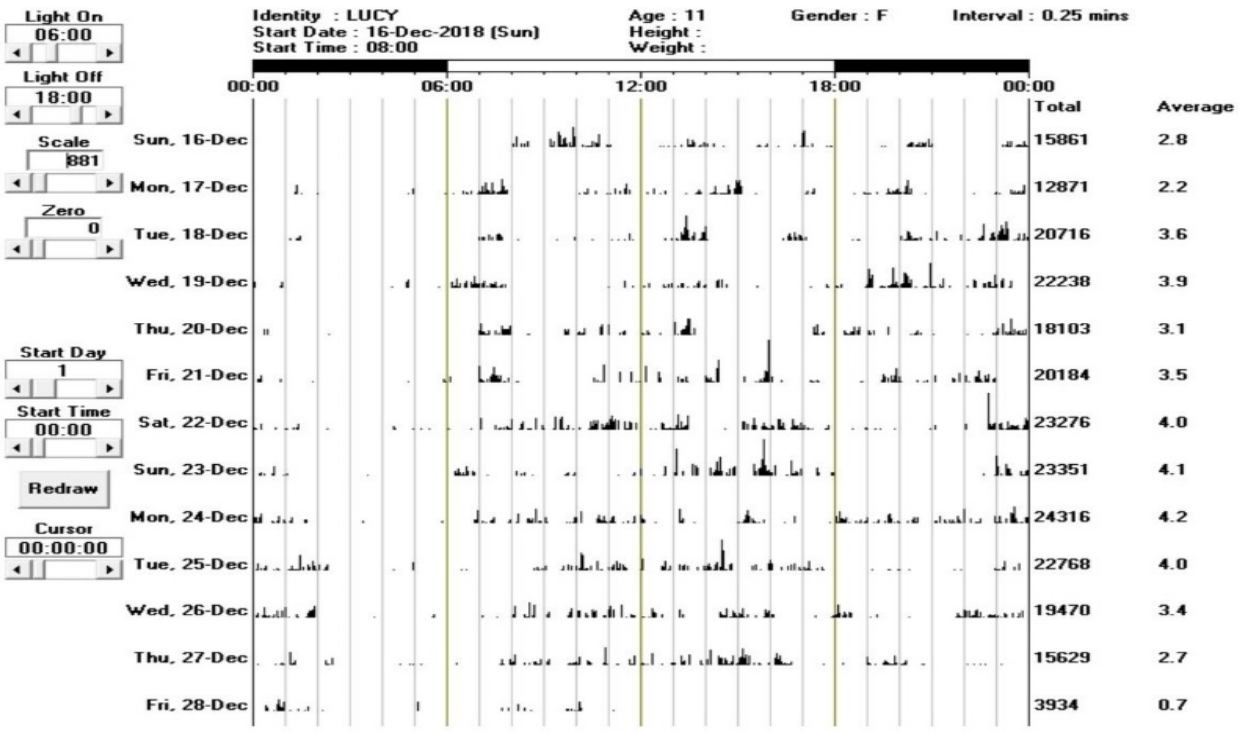

Figure 3.3: Representative graph Illustrating Activity Counts as Generated by the Activity Monitor

The graph shows total activity counts per day ("Total") as well as the average hourly activity count ("Average") for one of the study's participants.

3.3.5.4 Outcome Measures

Outcome measures included orthopaedic examination findings as well as subjective owner assessments of impaired mobility and QoL using the FMPI and VetMetrica questionnaires, respectively. Obtaining and analysing accelerometry data served as the first part and, thus, a proof of concept for a major study using exclusively BC study cats.

3.3.6 Variables

The 17 variables that were collected and subsequently considered for analysis are listed in Table 3.3. The cat's status reflected the absence (Control = 0) or presence (Case = 1) of owner-reported early DJD-related signs.

Table 3.3: Variables Used for Analysis of Orthopaedic Examination, Quality of Life Assessment and Activity Monitoring of Cats with Owner-reported Signs of Degenerative Joint Disease Over Six Years of Age

Variable Name	Variable Type	Variable Range	Final Categories
Age in Life Stages	Categorical	< 7 years	Prime
		≥ 7 – 11 years	Mature
		≥ 11 – 15 years	Senior
		≥ 15 years	Geriatric
Sex	Categorical	Male	Male
		Female	Female
Breed	Categorical	DSH	DSH, DLH and their crossbreeds
		DLH	
		Remaining specific breeds	Purebred
Neuter Status	Categorical	No	Entire
		Yes	Neutered
FMPI	Continuous	0 – 1	0 – 1
VetMetrica Vitality Domain	Continuous	0 – 70	0 – 70

Variable Name	Variable Type	Variable Range	Final Categories
VetMetrica Comfort Domain	Continuous	0 – 70	0 – 70
VetMetrica EWB Domain	Continuous	0 – 70	0 – 70
Owner Perception of QoL	Categorical	Very poor	Very poor
		Poor	Poor
		Good	Good
		Very good	Very good
Temperament Assessment	Categorical	0	Friendly
		1	
		2	
		3	Unfriendly
		4	
BCS (Assessed by Veterinary Surgeon)	Categorical	1	Not Overweight
		2	
		3	
		4	
		5	
		6	Overweight/Obese
		7	
		8	
		9	
Total Pain Score	Continuous	0 – 80	0 – 80
Total Crepitus Score	Continuous	0 – 32	0 – 32
Total Effusion Score	Continuous	0 – 24	0 – 24
Total Thickening Score	Continuous	0 – 28	0 – 28
Presence of Bilateral Pain	Categorical	Yes	Yes
		No	No
Number of Joints with Bilateral Pain	Continuous	0 – 8	0 – 8

Body condition score (BCS); Domestic long hair (DLH); Domestic short hair (DSH); Emotional wellbeing (EWB); Feline Musculoskeletal Pain Index (FMPI); Quality of life (QoL).

Age was regrouped into biologically relevant life stages which have clinical relevance in terms of the physical and behavioural changes that occur at different time points in cats' lives, thereby informing veterinary care

(Hoyumpa Vogt et al., 2010). These were: < 7 years = “Prime”, ≥ 7 – 11 years = “Mature”, ≥ 11 – 15 years = “Senior”, and ≥ 15 years = “Geriatric”.

As data were sparse for some of the lower BCS using the 9-point system (Bjornvad et al., 2011), cats were grouped for further analysis as “overweight/obese” for BCS 6–9, which included both overweight (6–7) and obese (8–9) cats, or “not overweight” for BCS 1–5, which included underweight (1–3) cats and cats of ideal weight (4–5).

Data were also sparse for the temperament assessment scores, therefore these were collapsed for analysis with 0–2 = “friendly”, or 3–4 = “unfriendly” (Jaeger et al., 2007).

Total appendicular and axial scores were generated for each cat by summing the pain score for each individual appendicular or axial joint with a possible range of 0–64 and 0–16, respectively, then a total pain score was created for each cat by summing the total appendicular and axial scores with a possible range of 0-80. Total crepitus, thickening and effusion (manipulation scores) were also generated for each cat by summing the score for each individual appendicular joint with a possible range of 0–32, 0–28 and 0–24, respectively.

Individual pain and manipulation scores were additionally grouped into “no pain” and “no abnormal signs” if 0, or “pain present” and “abnormal signs present” if ≥ 1, respectively. These scores were used in descriptive statistics to describe a) the number of joints with pain, crepitus, thickening, and effusion detected during orthopaedic examination, b) the most frequently affected appendicular and axial joints, and c) the frequency of bilateral pain. They were also used to compare the presence of bilateral pain as well as the number of joints with bilateral pain between the groups.

3.3.7 Statistical Analysis

Analyses were performed using SPSS (version 24.0.0.2, IBM Corporation, USA). Unless stated otherwise, an alpha value of ≤ 0.05 was set for statistical significance in all analyses, and an exact significance (2-tailed) is reported. Out of the 17 variables analysed, eight were continuous and nine were categorical. Continuous data were examined for normality using histograms and the Kolmogorov-Smirnov test; p-values ≥ 0.05 were required for data to be considered normally distributed. All continuous variables apart from Total Pain and VetMetrica Vitality Domain scores were non-normally distributed and, despite applying different transformations (logarithmic, square root and reciprocal), it was not possible to normalise them (Appendix O). Consequently, non-parametric statistical tests were used.

Group comparisons were performed using a Mann-Whitney or chi-square test if the variables were continuous or categorical, respectively. Fisher's exact test (FET) was used instead of the chi-square test when > 20% of cells had expected frequencies of < 5. A posthoc comparison using the Holm-Bonferroni correction (Holm, 1979) was performed to correct for the familywise error rate associated with multiple hypothesis testing. A corrected significance cut-off was calculated for each hypothesis as α/n – rank number of pair (by degree of significance) +1, where n = number of tests (Appendix P). The null hypothesis (there is no difference between the two groups of cats for the selected variable) was rejected when the p-value associated with each hypothesis was lower than the corrected p-value calculated using the Holm-Bonferroni correction. The measure of effect size (r) for the Mann-Whitney tests was calculated by dividing the z value from the test by the total number of observations; effect sizes between 0.1 – < 0.3, 0.3 – < 0.5 and ≥ 0.5 were considered small, medium, and large, respectively. Odds ratio (OR) and Cramér's V were used as measures of effect size on the results of chi-square and FET tests depending on the degrees of freedom (df), with effect sizes classified as small, medium, and large for Cramér's V, (Cohen, 1988).

Before machine learning of the accelerometer data could be carried out, the researcher imported the raw accelerometer data into an Excel spreadsheet for each cat. Information obtained from owner diaries was then

used to ascertain the duration that the collar and/or the device was not worn by each cat, this establishing missing accelerometer datapoints. Finally, the researcher prepared two spreadsheet containing each cat's metadata (unique identification number, Case or Control status, and age) as well as each cat's missing accelerometer datapoints. The remainder of the analysis including machine learning of the accelerometer data was undertaken by Axel Montout, PhD student of Professor Andrew Dowsey, Bristol Veterinary School, using the Python programming language and scikit-learn 0.22.1. A pre-processing pipeline was used to read each spreadsheet containing accelerometer data and link it to the metadata spreadsheet via the cat identification number, then extract the date, time, and activity counts (Figure 3.4). Missing datapoints were replaced with the value of -1 which is not generated by the accelerometer, allowing 14 full days of data per cat for analysis. Accelerometer data were binned into 10-minute intervals for analysis. It was unfortunately not possible to perform analysis using a higher resolution than this due to lack of computational power. Accelerometer data were Anscombe transformed to remove heteroscedasticity due to Poisson counting statistics, then log transformed to remove residual heteroscedasticity. This was followed by a Continuous Wavelet Transform which has been shown to decorrelate the period of activity from its intensity so that the artificial intelligence can discriminate on activity durations as well as intensities (McCamley et al., 2012). Linear Discriminant Analysis was used for dimensionality reduction, reducing the original number of dimensions to two whilst maintaining the most important features in the input array and maximising class separation (McLachlan, 2004). The dataset was then randomly divided into training (60%) and testing (40%) datasets, and logistic regression was used to predict each cat's class (status) with their age included as an additional variable at this stage. Each output was associated with a classification accuracy as well as two parameters for each class: accuracy and precision. Accuracy is the ratio of the number of correct predictions to the total number of predictions made, whereas precision is the ratio of the number of true positives divided by the sum of true and false positives. Recall for Class 0 (Controls) and Class 1 (Cases) represent the output's specificity and sensitivity, respectively.

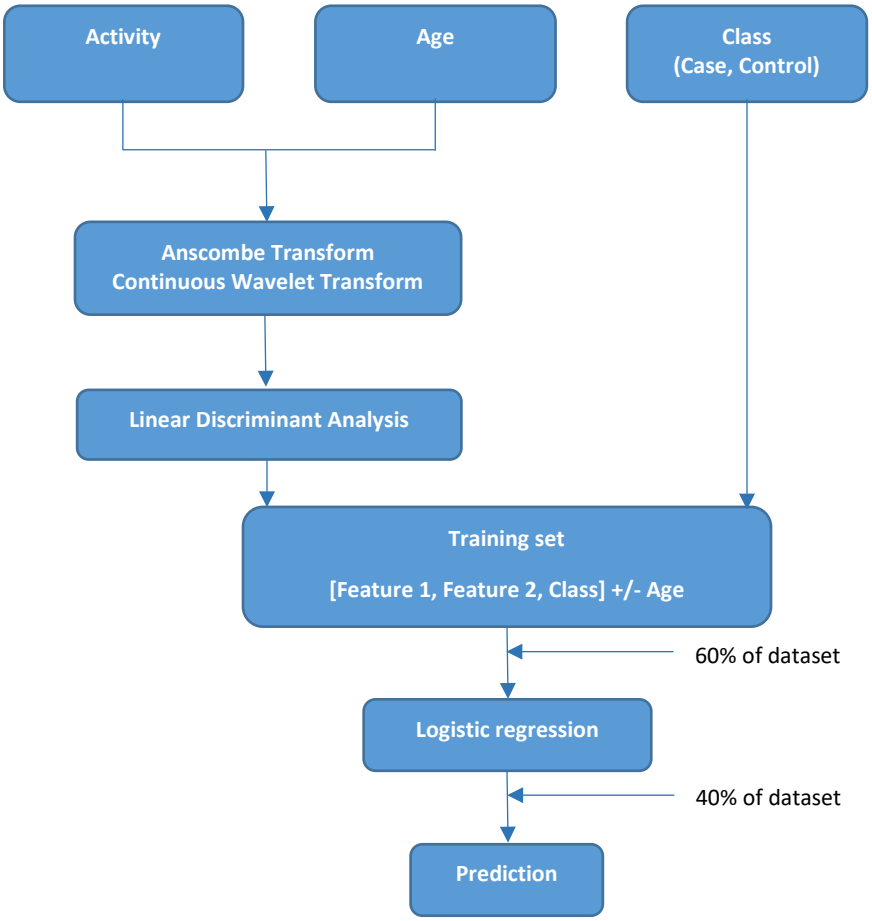

Figure 3.4: Diagram Illustrating the Pre-processing Pipeline and the Steps Followed for Machine Learning Analysis of the Accelerometer Data

3.4 Results

3.4.1 Participants

Demographic and eligibility data were obtained from the most recently completed BC study and inclusion questionnaires for BC and nBC participants, respectively. These were completed fully by all participating owners, resulting in no missing data in any of the demographic variables.

All 57 participating cats were neutered, 29 (50.9%) were male, and most (n = 30, 52.6%) belonged in the Mature life stage age group (Table 3.4). The majority of cats were of mixed breed (n = 43, 75.4%), with the remaining 14 purebred cats consisting of two (3.5%) of each for Bengal, British short hair and Burmese and one of each (1.7%) for Devon Rex, Exotic short hair, Malayan, Oriental short hair, Persian, Ragamuffin, Ragdoll and Snowshoe. Moreover, 51 (89.5%) cats lived in a single-cat household, and the remaining 6 (10.5%) lived in a household with a total of two cats. At the time of recruitment, most cats (n = 40, 70.2%) were not wearing a collar and were habituated to wearing one in due course.

Table 3.4: Demographic Data for n = 57 Cats

Variables		**N (%) of Cats**
Age in Life Stages	Prime	5 (8.8%)
	Mature	30 (52.6%)
	Senior	13 (22.8%)
	Geriatric	9 (15.8%)
Sex	Male	29 (50.9%)
	Female	28 (49.1%)
Neuter Status	Entire	0 (0.0%)
	Neutered	57 (100.0%)
Breed Category	DSH, DLH and their crossbreeds	43 (75.4%)
	Purebred	14 (24.6%)

Domestic long hair (DLH); Domestic short hair (DSH).

3.4.2 Pre-visit Measures

The FMPI and VetMetrica questionnaires were completed fully by 50 cat owners before the visit took place. Four and three owners, respectively, completed the FMPI and VetMetrica questionnaires approximately two weeks after the visit had taken place. Results for the continuous pre-visit measures are listed in Table 3.5. Most owners perceived their cat's QoL as "very good" (n = 40, 70.2%) or "good" (n = 17, 29.8%), whereas no owners perceived their cat's QoL as "poor" or "very poor".

Table 3.5: Pre-Visit Measures for n = 57 Cats

Variable	Range	Median	IQR
Feline Musculoskeletal Pain Index	0.64 – 1.00	1.00	0.97 – 1.00
VetMetrica Vitality Domain	26.5 – 64.0	49.8	44.6 – 55.1
VetMetrica Comfort Domain	30.1 – 59.6	44.2	39.2 – 57.2
VetMetrica Emotional Wellbeing Domain	34.4 – 58.8	51.9	45.6 – 56.3

Interquartile range (IQR).

3.4.3 Visit Measures

3.4.3.1 Temperament Assessment

There were no missing data for temperament assessment scores. These ranged from 0 to 4, with a median of 1 and an IQR of 0 – 2 (Table 3.6). Most cats scored 0 (n = 22, 38.6%) or 1 (n = 20, 35.1%). Seven cats (12.3%) were quite vocal when initially approached and even after they were given more time to acclimatise to the researcher's presence; however, they were happy to be handled and some were also kneading or purring. Consequently, the orthopaedic examination was performed without any stress to these cats and they were assigned a score of 3 to account for their more vocal nature. The score of 4 was assigned to a cat that was revealed to be extremely fearful of strangers when the researcher entered the house and therefore was not examined at all. Most cats (n = 49, 86%) were considered to have a friendly temperament towards the researcher (scores 0-2 inclusive).

Table 3.6: Temperament Assessment for n = 57 Cats

Variable Range	N (%) of Cats
0: Neutral attitude, purring, kneading	22 (38.6%)
1: Resistance to restraint	20 (35.1%)
2: Resistance to restraint, growling and hissing	7 (12.3%)
3: Resistance with biting and scratching, hissing, spitting, and vocalising	7 (12.3%)
4: Resistance with biting, scratching, vocalising, spitting, hissing, urinating, or defecating	1 (1.7%)

3.4.3.2 Body Condition Score (Assessed by Veterinary Surgeon)

There were no missing data for BCS. These ranged from 3 to 7 with a median of 5 and an IQR of 4.5 – 6. Most cats (n = 18, 31.6%) had a BCS of 5 (Table 3.7, Figure 3.5). When grouped according to their score, 32 cats (56.1%) were not considered overweight and 25 cats (43.9%) were considered overweight/obese.

Table 3.7: Body Condition Score (Assessed by Veterinary Surgeon) for n = 57 Cats

Variable		N (%) of Cats
Body Condition Score (Assessed by Veterinary Surgeon)	3	1 (1.8%)
	4	13 (22.8%)
	5	18 (31.6%)
	6	15 (26.3%)
	7	10 (17.5%)

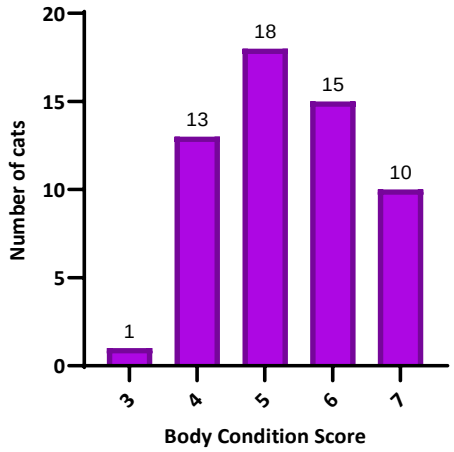

Figure 3.5: Body Condition Score (Assessed by Veterinary Surgeon) for n = 57 Cats

3.4.3.3 Orthopaedic Examination

There were only 30/1140 (2.63%), 26/912 (2.85%), 12/684 (1.75%), and 14/798 (1.75%) missing pain, crepitus, effusion, and thickening scores, respectively, as a result of the generally friendly cat temperament. These included missing scores for both hip joints in five cats, and missing scores for all 20 joints (16 appendicular and four axial joints) in one cat due to its temperament. Consequently, only data from 56 cats were included in the analysis of orthopaedic examination data. The number of joints and spinal segments with or without clinically detected abnormalities on orthopaedic examination are summarised in Table 3.8.

Table 3.8: Prevalence of Abnormalities Detected During Orthopaedic Examination of the Appendicular and Axial Skeleton in n = 56 Cats

	N (%) of Joints with Pain	N (%) of Joints with Crepitus	N (%) of Joints with Effusion	N (%) of Joints with Thickening	Joints without Abnormalities	Total Number of Assessed Joints
Right Manus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	56	56
Right Carpus	3 (5.4%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	52	56
Right Elbow	40 (71.4%)	6 (10.7%)	0 (0.0%)	14 (25.0%)	15	56
Right Shoulder	8 (14.3%)	0 (0.0%)		0 (0.0%)	48	56
Right Pes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	56	56
Right Tarsus	39 (69.6%)	3 (5.4%)	0 (0.0%)	1 (1.8%)	17	56
Right Stifle	44 (78.6%)	7 (12.5%)	0 (0.0%)	28 (50.0%)	11	56
Right Hip	40 (78.4%)	5 (9.8%)			11	51
Left Manus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	56	56
Left Carpus	4 (7.1%)	4 (7.1%)	0 (0.0%)	0 (0.0%)	50	56
Left Elbow	36 (64.3%)	4 (7.1%)	0 (0.0%)	4 (7.1%)	19	56
Left Shoulder	6 (10.7%)	0 (0.0%)		0 (0.0%)	50	56
Left Pes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	56	56
Left Tarsus	21 (37.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	35	56
Left Stifle	41 (73.2%)	2 (3.6%)	0 (0.0%)	4 (7.1%)	15	56
Left Hip	37 (72.5%)	1 (2.0%)			14	51
Cervical Spine	0 (0.0%)				56	56
Thoracic Spine	46 (82.1%)				10	56
Lumbar Spine	28 (50.0%)				28	56
Lumbosacral Spine	13 (23.2%)				43	56

Figure 3.6 summarises the orthopaedic examination findings for the appendicular skeleton. No manus or pes joint was found to be painful on manipulation. Pain was detected in the hip, stifle, elbow, and tarsus in descending frequency. Crepitus was most frequently detected in the elbow and stifle joint, whereas thickening was most frequently identified in the stifle joint. Effusion was not detected in any joint. The thoracic and lumbar segments were the most frequently painful segments in the axial skeleton (Figure 3.7).

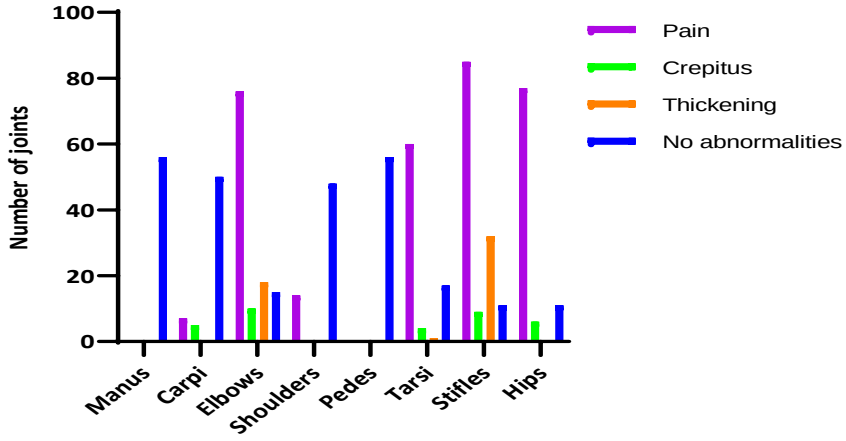

Figure 3.6: Summary of Abnormalities Detected During Orthopaedic Examination of the Appendicular Skeleton in n = 56 Cats

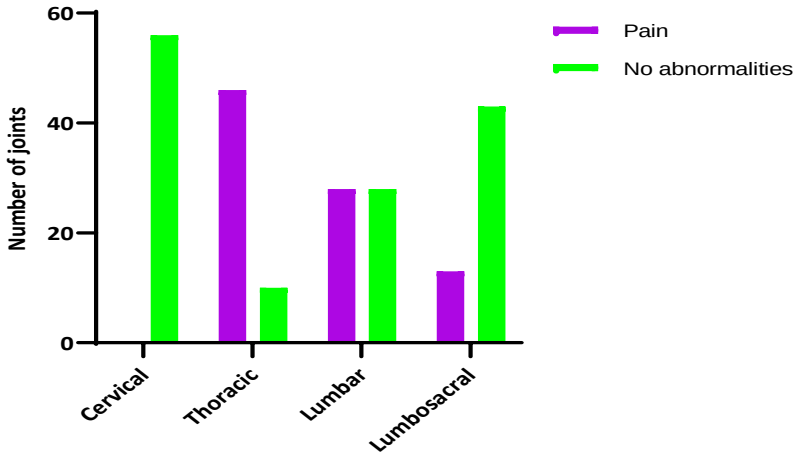

Figure 3.7: Prevalence of Pain Detected During Orthopaedic Examination of the Axial Skeleton in n = 56 Cats

3.4.3.3.1 Pain and Manipulation Scores

Total pain score ranged from 0 to 27 with a median of 15 and an IQR of 8.5 – 19. Total crepitus score ranged from 0 to 4 with a median of 0 and an IQR of 0 – 1, whereas total thickening score ranged from 0 to 4 with a median of 1 and an IQR of 0 – 2.

3.4.3.3.2 Bilateral Pain

Bilateral pain was most frequently detected in the stifle and hip joint, followed by the elbow and tarsus joint (Table 3.9).

Table 3.9: Prevalence of Bilateral Pain in Each Joint Type in n = 56 Cats

	Carpus N (%) of Joints	Elbow N (%) of Joints	Shoulder N (%) of Joints	Tarsus N (%) of Joints	Stifle N (%) of Joints	Hip N (%) of Joints
Yes	0 (0%)	29 (51.8%)	1 (1.8%)	17 (30.4%)	36 (64.3%)	35 (62.5%)
No	56 (100%)	27 (48.2%)	55 (98.2%)	39 (69.6%)	20 (35.7%)	21 (37.5%)

The number of joints affected with bilateral pain ranged from 0 to 5 with a median of 2 and an IQR of 1 – 3. Only 10 (17.9%) of cats did not have bilaterally detected pain in any joint, whereas the remaining 46 cats had one (n = 9, 16.1%), two (n = 12, 21.4%), three (n = 16, 28.6%), four (n = 8, 14.3%), and five (n = 1, 1.8%) bilaterally affected joints (Figure 3.8).

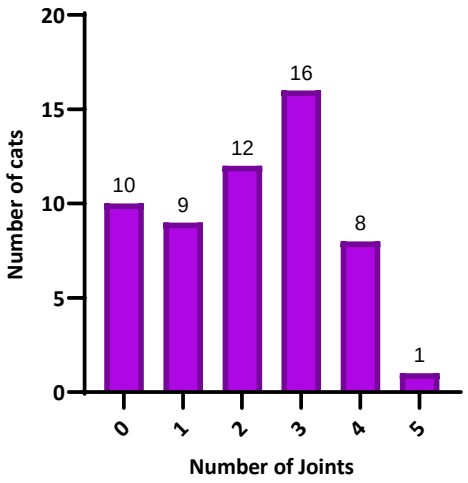

Figure 3.8: Total Number of Joints Affected with Bilateral Pain in n = 56 Cats

3.4.4 Group Comparisons

3.4.4.1 Participants

Mobility score ranged from 0 to 13 (Figure 3.9) with a median of 3 (IQR = 0 – 4). All 27 Control cats had a MS of 0 and the 30 Case cats had a median MS of 4 (IQR = 3.75 – 6).

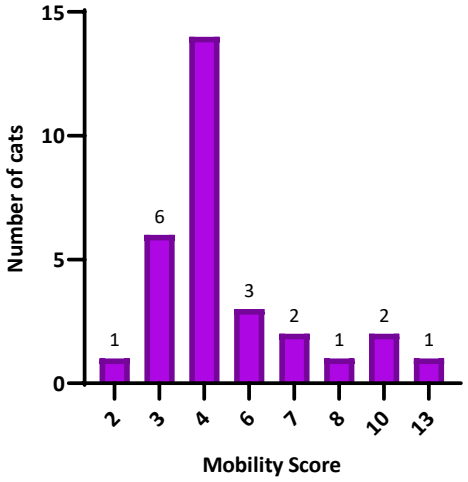

Figure 3.9: Owner-reported Mobility Score for n = 30 Case Cats

Neuter status was not analysed statistically as all cats were neutered. No significant difference was found between the two groups in terms of their demographic variables (Table 3.10). These were age in life stages (p = 0.079), sex (p = 0.11), and breed category (p = 0.765).

Table 3.10: Group Comparisons for Demographic Data in n = 57 Cats

		All Cats N (%) of Cats	Cases N (%) of Cats	Controls N (%) of Cats	Between Groups Analysis
Age in Life Stages	Prime	5 (8.8%)	3 (10.0%)	2 (7.4%)	FET = 6.74, p = 0.079 Cramér's V (4) = 0.348
	Mature	30 (52.6%)	11 (36.7%)	19 (70.4%)	
	Senior	13 (22.8%)	9 (30.0%)	4 (14.8%)	
	Geriatric	9 (15.8%)	7 (23.3%)	2 (7.4%)	
Sex	Male	29 (50.9%)	12 (40.0%)	17 (63.0%)	$\chi2$ (1) = 2.99, p = 0.11 OR = 2.55
	Female	28 (49.1%)	18 (60.0%)	10 (37.0%)	
Breed Category	DSH, DLH and their	43 (75.4%)	22 (73.3%)	21 (77.8%)	$\chi2$ (1) = 0.151, p = 0.765 OR = 0.78
	Purebred	14 (24.6%)	8 (26.7%)	6 (22.2%)	

Domestic long hair (DLH); Domestic short hair (DSH); Fisher's exact test (FET); Odds Ratio (OR). Corrected significance cut-off values associated with each hypothesis testing are: Age in Life Stages = 0.01, Sex = 0.0125, Breed Category = 0.05.

3.4.4.2 Pre-visit Measures

There was a significant difference and a moderate effect size when comparing FMPI scores (p = 0.003); Case cats scored lower than Control cats, signifying a higher degree of impaired mobility. There was also a significant difference and a moderate effect size for Comfort (p = 0.002) domain scores, with Case cats scoring lower than Control cats; no statistical difference was detected for Vitality and EWB domain scores (Table 3.11, Figure 3.10).

Table 3.11: Group Comparisons for Pre-Visit Measures in n = 57 Cats

	All Cats Median (IQR)	Cases Median (IQR)	Controls Median (IQR)	Between Groups Analysis
FMPI	1.00 (0.97-1.00)	0.98 (0.93-1.00)	1.00 (0.99-1.00)	U = 236.50, z = -2.917, p = 0.003*, r = -0.39
VetMetrica Vitality Domain	49.8 (44.6-55.1)	46.9 (40.2-53.2)	51.7 (48.60-58.8)	U = 242.00, z = -2.605, p = 0.009, r = -0.35
VetMetrica Comfort Domain	44.2 (39.2-57.2)	41.3 (36.0-46.0)	52.0 (40.4-59.6)	U = 212.50, z = -3.099, p = 0.002*, r = -0.41
VetMetrica EWB Domain	51.9 (45.6-56.3)	51.1 (43.6-55.3)	55.8 (49.2-57.0)	U = 258.50, z = -2.349, p = 0.018, r = -0.31

Emotional wellbeing (EWB); Interquartile range (IQR).
*Corrected significance cut-off values associated with each hypothesis testing are: FMPI = 0.005, Vitality = 0.0071, Comfort = 0.0042 and EWB = 0.0083. Results designated with a * were statistically significant.*

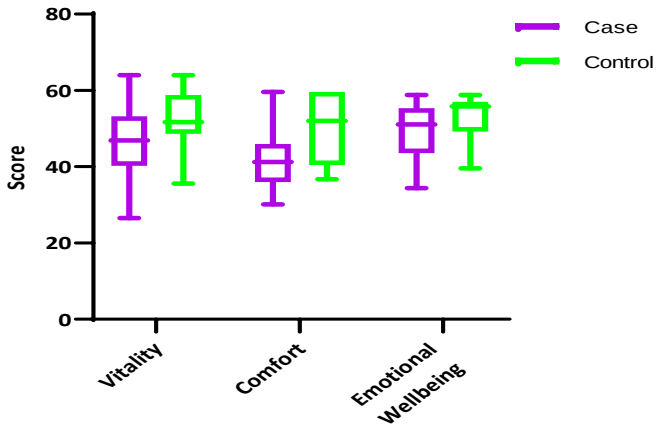

Figure 3.10: Group Comparisons for VetMetrica Domain Scores in n = 57 Cats

Owner perception of QoL was not statistically analysed as two out of the four categories ("very poor" and "poor") had no data.

3.4.4.3 Visit Measures

3.4.4.3.1 Temperament Assessment

There was no significant difference between the two groups (p = 0.258) for the number of cats defined as friendly or unfriendly by the researcher (Table 3.12, Figure 3.11).

Table 3.12: Group Comparisons for Temperament Assessment in n = 57 Cats

	All Cats N (%) of Cats	**Cases N (%) of Cats**	**Controls N (%) of Cats**	**Between Groups Analysis**
Friendly Temperament	49 (86%)	24 (80%)	25 (92.6%)	FET = 1.87, p = 0.258, OR = 3.125
Unfriendly Temperament	8 (14%)	6 (20%)	2 (7.4%)	

Fisher's exact test (FET); Odds Ratio (OR).
The corrected significance cut-off value associated with the hypothesis testing is 0.0167.

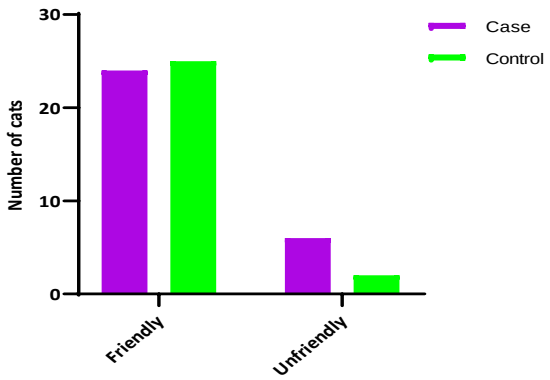

Figure 3.11: Group comparisons for Temperament Assessment in n = 57 Cats

3.4.4.3.2 Body Condition Score (Assessed by Veterinary Surgeon)

There was no significant difference between the two groups (p = 0.425) for the number of cats defined as overweight/obese or not overweight (Table 3.13, Figure 3.12).

Table 3.13: Group Comparisons for Body Condition Score (Assessed by Veterinary Surgeon) in n = 57 Cats

		All Cats N (%) of Cats	Cases N (%) of Cats	Controls N (%) of Cats	Between Groups Analysis
BCS (Assessed by Veterinary Surgeon)	Not Overweight	32 (56.1%)	14 (46.7%)	17 (63.0%)	$\chi 2$ (1) = 0.97, p = 0.425, OR = 1.7
	Overweight/Obese	25 (43.9%)	15 (50.0%)	10 (37.0%)	

Body Condition Score (BCS); Odds Ratio (OR).
The corrected significance cut-off value associated with the hypothesis testing is 0.025.

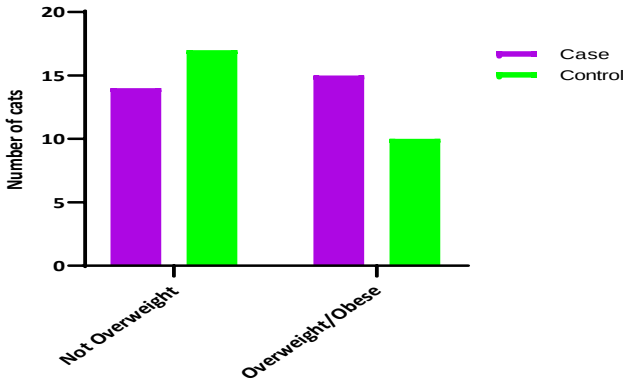

Figure 3.12: Body Condition Score (Assessed by Veterinary Surgeon) in n = 57 Cats

3.4.4.3.3 Orthopaedic Examination

3.4.4.3.3.1 Pain and Manipulation Scores

There was a significant difference when comparing total pain ($p < 0.0001$), crepitus ($p = 0.002$), and thickening ($p = 0.003$) scores, with Case cats scoring higher than Control cats (Table 3.14, Figure 3.13). The observed effect size was large for total pain score and moderate for total crepitus and thickening scores.

Table 3.14: Group Comparisons for Total Pain and Manipulation Scores in n = 56 Cats

Scores	All Cats Median (IQR)	Cases Median (IQR)	Controls Median (IQR)	Between Groups Analysis
Total Pain Score	15 (8.50–19)	18 (15.5–20)	11 (4–15)	U = 127.50, z = -4.338, p < 0.0001*, r = -0.58
Total Crepitus Score	0 (0–1)	1 (0–1)	0 (0–0)	U = 223.00, z = -3.095, p = 0.002*, r = -0.41
Total Thickening Score	1 (0–2)	1 (0–2)	0 (0–1)	U = 224.50, z = -2.902, p = 0.003*, r = -0.39

Interquartile range (IQR).
*Corrected significance cut-off values associated with each hypothesis testing are: Total Pain = 0.0036, Total Crepitus = 0.0045) and Total Thickening = 0.0056. Results designated with a * were statistically significant.*

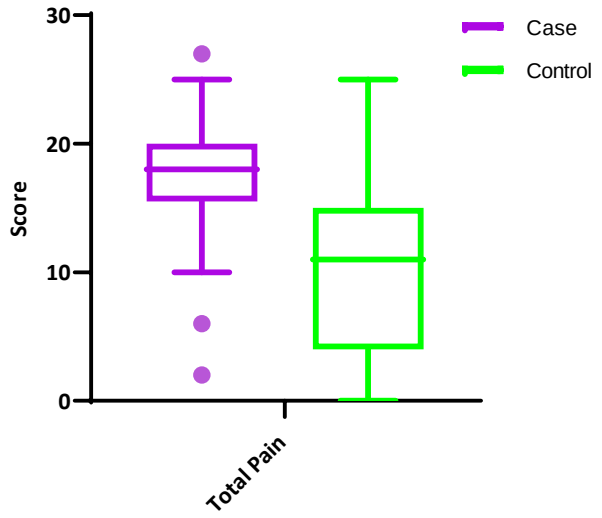

Figure 3.13: Group Comparisons for Total Pain Score in n = 57 Cats

3.4.4.3.3.2 Bilateral Pain

The presence of bilateral pain was significantly different between the two groups (p = 0.005), with Case cats being 14 times more likely to have bilateral pain compared to Control cats (Table 3.15, Figure 3.14).

Table 3.15: Group Comparisons for the Prevalence of Bilateral Pain in n = 56 Cats

		All Cats N (%) of Cats	Cases N (%) of Cats	Controls N (%) of Cats	Between Groups Analysis
Bilateral Pain	Yes	46 (82.1%)	28 (96.6%)	18 (66.7%)	FET = 8.51, p = 0.005*, OR = 14
	No	10 (17.9%)	1 (3.4%)	9 (33.3%)	

Fisher's exact test (FET); Odds Ratio (OR).
*The corrected significance cut-off value associated with the hypothesis testing is 0.0063. Results designated with a * were statistically significant.*

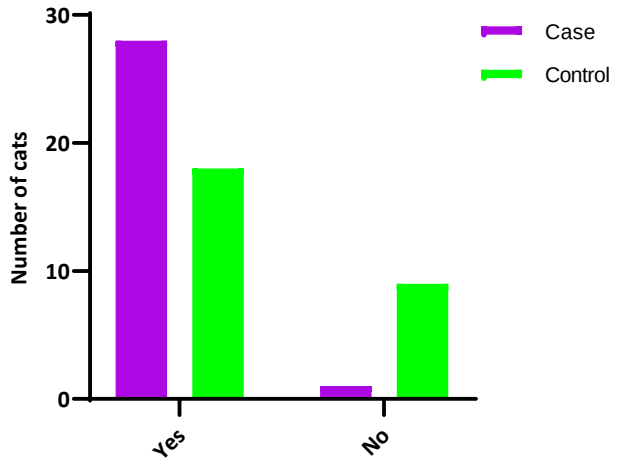

Figure 3.14: Group Comparisons for the Prevalence of Bilateral Pain in n = 56 Cats

The prevalence of bilateral pain in different joints for the two groups, Cases and Controls, is shown in Table 3.16.

Table 3.16: Prevalence of Bilateral Pain in Different Joints for n = 30 Case and n = 27 Control Cats

		All Cats N (%) of Joints	Cases N (%) of Joints	Controls N (%) of Joints
Carpus	Yes	0 (0%)	0 (0%)	0 (0%)
	No	56 (100%)	29 (100%)	27 (100%)
Elbow	Yes	29 (51.8%)	20 (69%)	9 (33.3%)
	No	27 (48.2%)	9 (31%)	18 (66.7%)
Shoulder	Yes	1 (1.8%)	1 (3.4%)	0 (0%)
	No	55 (98.2%)	28 (96.6%)	27 (100%)
Tarsus	Yes	17 (30.4%)	11 (37.9%)	6 (22.2%)
	No	39 (69.6%)	18 (62.1%)	21 (77.8%)
Stifle	Yes	36 (64.3%)	25 (86.2%)	11 (40.7%)
	No	20 (35.4%)	4 (13.8%)	16 (59.3%)
Hip	Yes	35 (68.6%)	22 (81.5%)	13 (54.2%)
	No	16 (28.1%)	5 (18.5%)	11 (45.8%)

There was a significant difference (p = 0.001) and a moderate effect size when comparing the number of joints affected with bilateral pain between the two groups, with Case cats having more affected joints than Control cats (Table 3.17, Figure 3.15).

Table 3.17: Group Comparisons for the Number of Joints Affected with Bilateral Pain in n = 56 Cats

Number of Joints	All Cats N (%) of Cats	Cases N (%) of Cats	Controls N (%) of Cats	Between Groups Analysis
0	10 (17.9%)	1 (3.4%)	9 (33.3%)	
1	9 (16.1%)	3 (10.3%)	6 (22.2%)	
2	12 (21.4%)	7 (24.1%)	5 (18.5%)	
3	16 (28.6%)	11 (37.9%)	5 (18.5%)	
4	8 (14.3%)	6 (20.7%)	2 (7.4%)	
5	1 (1.8%)	1 (3.4%)	0 (0.0%)	
Median (IQR)	2 (1–3)	3 (2–3.5)	1 (0–3)	U = 189.5, z = -3.391, p = 0.001*, r = -0.45

Interquartile Range (IQR).

*The corrected significance cut-off value associated with the hypothesis testing is 0.0038. Results designated with a * were statistically significant.*

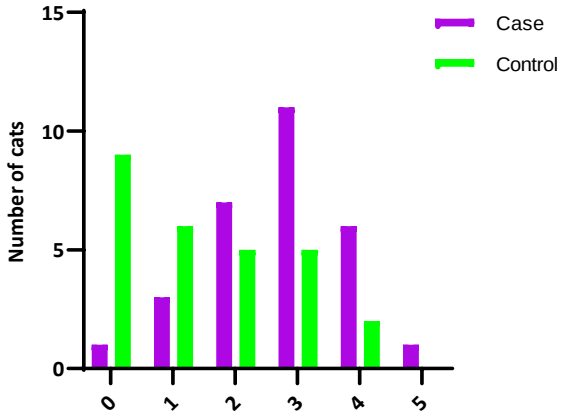

Figure 3.15: Group Comparisons for the Number of Joints Affected with Bilateral Pain in n = 56 Cats

3.4.4.4 Accelerometry

It was not possible to download the data from the accelerometers in two occasions, and therefore activity data from only 55 cats were included in the analysis. The accelerometer and/or collar fell off or were removed in 12 cats (21.4%) for variable durations resulting in missing data points (Appendix Q).

For the analysis, the log transform was enabled or disabled, then age was included or excluded, resulting in four different combinations: “log_enabled”, “log_disabled”, “log_enabled+age”, and “log_disabled+age”. The outputs (Figure 3.16) show that the accuracy was high for all combinations (86.4% to 90.9%), however enabling the log transform resulted in accuracy improving from 86.4% to 90.9%. Accuracy was not improved by the addition of age as a covariate. Precision was 91% for the Control group and 90% for the Case group in the “log_enabled” output, whereas Specificity was 91% and sensitivity was 90%.

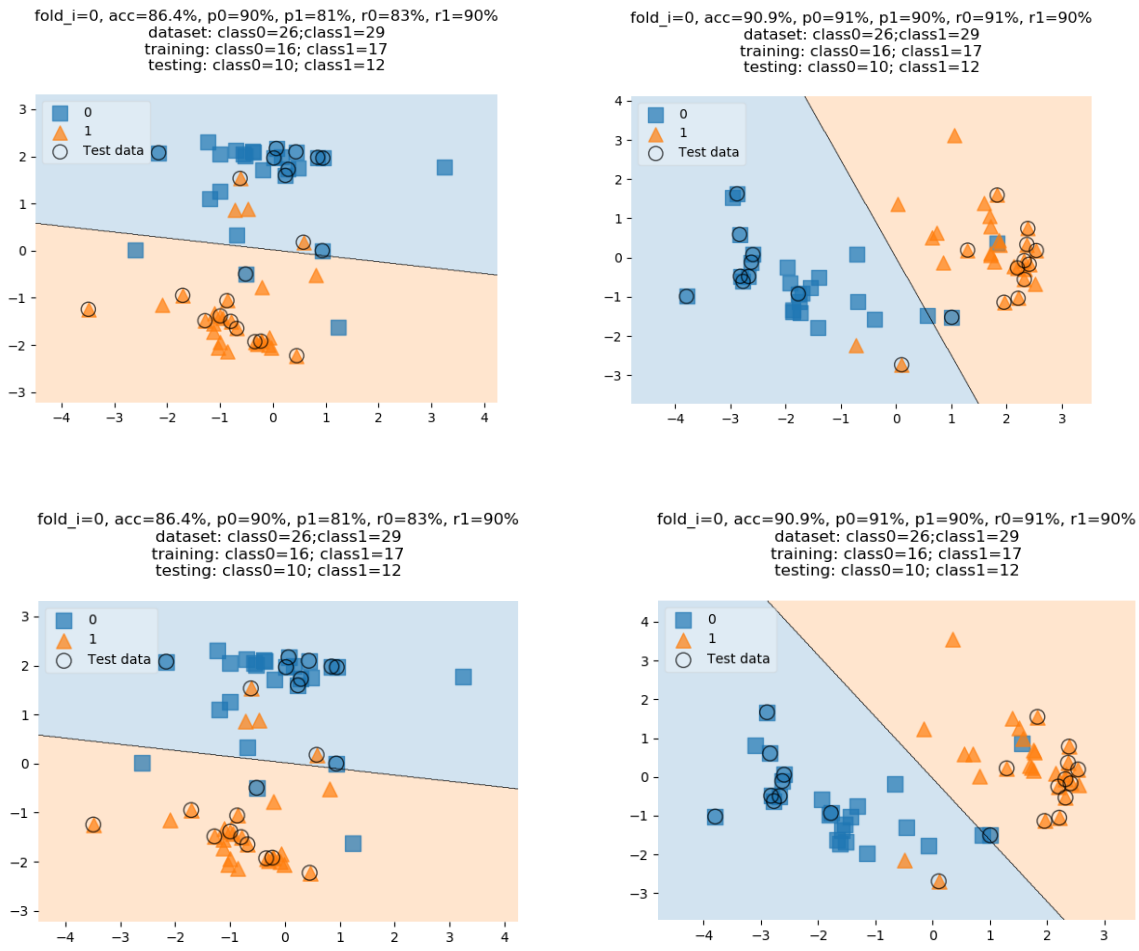

Figure 3.16: Accelerometer Outputs

(top-left) "log_disabled"; (top-right) "log_enabled"; (bottom-left) "log_disabled+age"; (bottom-right) "log_enabled+age"

Controls (0) are represented with blue squares and Cases (1) are represented with orange triangles. There were 10 Controls and 12 Cases in the training dataset, and 16 Controls and 17 Cases in the testing dataset (circled). Precision (p) is the ratio of the number of true positives divided by the sum of true and false positives; this is represented by the ratio of blue squares against the blue background for Controls (p0) and the ratio of orange triangles against the orange background (p1) for Cases (p1). Accuracy (acc) is the ratio of the number of correct predictions to the total number of predictions made. Recall for Controls (r0) and Cases (r1) represent the output's specificity and sensitivity, respectively.

3.5 Discussion

This study confirmed the initial hypothesis that early DJD-related pain has a significant impact on the QoL of affected cats. It additionally demonstrated that changes in joint health as detected by orthopaedic examination reflected owner-reported mobility changes, and that accelerometers were almost as sensitive as owners in detecting early signs of DJD-related pain in cats. Although multiple studies have compared the activity profiles of healthy cats to those with DJD using both subjective and objective tools, the cats in these studies had well-established DJD which was also confirmed using different imaging modalities (Gruen et al., 2015, Guillot et al., 2012, Lascelles et al., 2007c). On the contrary, this is the first study where the activity profiles of healthy cats and cats with owner-reported early DJD-related signs were assessed using prospectively collected data from subjective owner assessment questionnaires, orthopaedic examination, and accelerometers.

The FMPI has been established as a CMI with the ability to confidently differentiate between healthy cats and cats with both clinically and radiographically confirmed DJD (Benito et al., 2013a). Nevertheless, this is the first time that the FMPI was used to and was successful in detecting subtle differences between healthy cats and cats with early signs of DJD as evidenced by the significantly lower FMPI scores of Case cats compared to Control cats. This further validates FMPI as a useful tool that can be used in the clinical setting to assist with the earlier diagnosis of DJD.

VetMetrica scores were also significantly lower in Case cats compared to Control cats in the Comfort domain, , suggesting that even the lower degree of DJD-related pain experienced by cats with early DJD has a significant impact on the physical aspect of their quality of life. One possible explanation for the lack of a statistically detected difference between groups for the Vitality and EWB domain scores could be that owners have difficulty in distinguishing early DJD-related changes affecting the mental and emotional aspects of their cat's quality of life. This is the first time that this HRQoL instrument has been used in a population with early signs of DJD-related pain and no comorbidities, however this study's findings suggest that further refinement of the scoring algorithm may be indicated, especially in relation to items loading to more than one domain.

The temperament of cats as assessed by the researcher was not significantly different between Case and Control cats, contrary to previous studies where cats with higher pain scores were shown to have an unfriendly temperament (Lascelles et al., 2012, Stadig et al., 2019). This could be explained by the fact that the cats in those studies had well-established DJD rather than early signs of DJD-related pain, as was the case with the cats of the present study. Another point to note would be the fact that, similarly to QoL, temperament is a multidimensional concept (Ha and Ha, 2017), and therefore a single question may not be able to measure it reliably.

All pain and manipulation scores obtained during the orthopaedic examination were significantly higher in Case cats compared to Control cats. In addition, bilateral pain was detected in at least one joint in almost all Case cats, and Case cats were 14 times more likely to suffer from bilateral pain compared to Control cats. The number of joints where pain was detected bilaterally was also significantly higher in Case cats. These findings illustrate that, when performed in a consistent and systematic manner, orthopaedic examination is a valuable tool in the early diagnosis of DJD. Moreover, the results relating to bilateral pain further reinforce the previous belief that bilateral disease is a core component of feline DJD. Nevertheless, the higher prevalence of bilateral disease reported in this study should be interpreted with caution as it was a direct reflection of bilateral pain detected exclusively during orthopaedic examination. This is contrary to previous studies where the prevalence of bilateral DJD was estimated based on radiographic studies with/without orthopaedic examination findings (Clarke and Bennett, 2006, Godfrey and Vaughan, 2018, Godfrey, 2005, Kimura et al., 2020, Lascelles et al., 2010b, Slingerland et al., 2011).

Machine learning of the accelerometer data classified accurately 90.9% of all cats with a precision of 91% for the Control group and 90% for the Case group. Interestingly, adding age as a covariate did not improve accuracy for either group, illustrating that the accelerometry data already intrinsically contain the information that age provides. Nevertheless, owners in this study were highly motivated and may have been able to detect changes in their cats' mobility more accurately than most cat owners. In any case, accelerometry appears to provide a good reflection of owner-reported mobility changes and is a useful alternative, particularly with less observant

owners. This finding supports the use of accelerometry for the earlier detection of DJD in the clinical setting. Additional research investigating the use of accelerometry in cats with early signs of DJD-related pain is in progress and will be published soon by the researcher.

One of the limitations of this study's design was the fact that, like the first study, it depended on owner-reported data which could have introduced bias. Recruitment of cats outside the BC study cohort was only possible after the owners contacted the researcher themselves, possibly introducing response bias. Moreover, questionnaire data were used to classify cats as Cases or Controls as well as to assess impaired mobility (FMPI) and QoL (VetMetrica), possibly introducing reporting bias. Reporting bias could have been partially mitigated if the veterinary records had been checked for exclusion criteria that had not been reported by owners, such as the diagnosis of any condition that could influence mobility or the administration of any anti-inflammatory or analgesic medications. Unfortunately, this was not possible within the study's time frame. In addition to reporting bias, questionnaire completion could have been affected by measurement bias, with owners not wanting to admit that their cats were showing signs of impaired mobility or QoL. Notwithstanding the fact that the researcher did not share any information regarding the cats' orthopaedic examination or activity monitoring at any point during the study, subconscious clues may have been picked up by the owners; this could have biased their responses to the seven pre-visit questionnaires which were completed after the visit took place. Every effort was made to minimise interviewer bias by blinding the researcher to each cat's classification as Case or Control and demographic data until data analysis began. This bias could be mitigated in future studies by having different veterinary surgeons perform the orthopaedic examination whilst following a standardised protocol to minimise inter-observer variability. Even though owners were advised to keep their cat's routine unchanged, they may have introduced e.g. more play sessions with their cat, thereby skewing the accelerometer results to reflect a more active lifestyle than normal. Accelerometer removal was reported in one fifth of the study's cats but, unless noted immediately, owners may have been inaccurate in recording the time when the device or the collar fell off and were replaced, thus introducing recall bias. Owners could have additionally omitted time periods when the device fell off for fear of being excluded from the study. Selection

bias can also not be excluded even though every attempt was made to randomly select cats to participate in this study. Another limitation relates to the fact that approximately 10% of the recruited cats belonged to the same households, therefore not all study cats were independent. This study's population was generally similar to the UK cat population attending primary-care veterinary practices apart from the proportion of purebred cats which was higher (~25%) than the reported 11% (O'Neill et al., 2015). Owners in this study were possibly more motivated than owners attending primary-care veterinary practices since they were willing to complete several questionnaires, allow the researcher to visit and examine their cat as well as agree to the placement of an activity monitor on their cat for two weeks. Owners of pedigree cats may also be considered more motivated than the general cat-owning population as they have been shown to focus more on the companionship and health of their cats (Plitman et al., 2019) than owners of non-pedigree cats, which could in turn have made them more likely to wish to participate in this study. The Case and Control groups did not differ significantly in terms of their demographic characteristics (age in life stages, sex, neuter status, breed category). Although the initial consideration was to use each cat's age as a continuous variable, most owners were only able to provide an estimate rather than an accurate age. Grouping the participants' age according to life stages had a holistic clinical basis (Hoyumpa Vogt et al., 2010) and made it possible to recruit enough cats whilst making allowances for age estimates. With regards to omission bias, the decision to exclude cats less than six years of age from this study and with it approximately half the UK cat population (Sanchez-Vizcaino et al., 2017) was made based on the mean age of the reported prevalence of radiographic DJD (Tables 1 and 2). Cats with unrestricted outdoor access were excluded to avoid the risk of losing the activity monitor. Although 90.9% of UK cats are reported to have outdoor access (Murray and Gruffydd-Jones, 2012), there is no distinction between cats with unrestricted outdoor access and cats that go outside on a lead or an enclosed garden; the latter were not excluded from this study. Cats were also excluded if they lived further than 100 miles from Bristol Veterinary School as it was not possible to visit outside that radius based on the study's allocated time frame and budget and, similarly to humans, there may be differences in the geographical prevalence of DJD between populations as a result of environmental or genetic factors (Zhang and Jordan, 2010). Despite not achieving the optimum

recruitment number of 30 cats per group, the study was able to detect significant differences between the two groups, suggesting that 27 cats per group may be sufficient for future case-control studies in cats with early signs of DJD-related pain.

3.6 Conclusion

The significant impact of even early DJD-related pain on the QoL of affected cats further supports the need to diagnose DJD earlier. Being able to recognise signs of mobility impairment sooner would allow interventions aimed at slowing DJD progression, thereby improving feline health and welfare. This study demonstrated that orthopaedic examination findings agree with information obtained from owners, and both can be used to confidently differentiate cats with early signs of DJD-related pain from healthy cats in the consult room. Accelerometry was also able to discriminate between the two groups with great precision, illustrating that this objective outcome measure has great potential and further studies on its clinical use are warranted.

4. CONCLUSIONS AND FUTURE WORK

The risk factor analysis study for owner-reported signs of early DJD at six years of age not only evaluated early life risk factors for the first time, but also utilised prospective data from a longitudinal cohort study, further expanding research on feline DJD by identifying novel risk factors for its development. Cats that were entire at six months of age, cats that were obese at six years of age, cats with outdoor access and cats with a history of trauma were more likely to have early DJD-related changes in owner-reported mobility at six years of age. Further research is needed to determine if other aspects of a cat's husbandry, diet, lifestyle, and clinical history are implicated in the development of DJD. Additional research on the link between chronic inflammatory processes such as DJD, CKD and dental disease is also warranted. Future risk factor analysis on older BC study cats could corroborate the findings of the present study and identify additional risk factors for the development of DJD, as well as compare owner-reported signs of early DJD to well-established DJD.

The need to diagnose DJD earlier is further supported by the significant impact of even early DJD-related pain on the comfort aspect of the QoL of affected cats. This study's findings reinforced the belief that owners can recognise DJD-related changes in the activity profile of their cats, and that orthopaedic examination findings accurately reflect early DJD-related changes in owner-reported mobility. Moreover, the use of accelerometry identified these owner-reported changes with great precision, and further analysis already underway by the researcher aims to identify the aspects of a cat's activity that discriminated between cats with and without owner-reported signs of early DJD. Future studies using the same cats and/or a larger sample of cats with radiographically confirmed joint changes would further substantiate this study's findings with regards to owner report and orthopaedic examination, as well as validate the ability of accelerometry data to predict the presence of DJD. Further research may also include an intervention study to examine whether preventative measures, if implemented at early stages of DJD, would prove effective in delaying or reversing further disease progression.

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6. APPENDICES

APPENDIX A FELINE MUSCULOSKELETAL PAIN INDEX

NC STATE
Veterinary Medicine
Comparative Pain
Research Laboratory

NOTES TO ACCOMPANY THE FMPI CLINICAL METROLOGY INSTRUMENT

Conditions of use:

- The FMPI is designed as a Clinical Metrology Instrument (Questionnaire) for the assessment of Feline Musculoskeletal Pain. It can be used in clinical research studies, and also by practitioners for individual case assessment.
- Use of this questionnaire in a commercial setting (e.g. company funded clinical trials) requires the permission for use of the FMPI under license from North Carolina State University.
- The FMPI will be acknowledged in any publication or report by citing the appropriate reference.
- The FMPI will be used only in the form presented here, and the format, wording and order of the questions and responses will not be changed.
- The FMPI must not be given to others.
- The FMPI must not be sold in any form.

The FMPI is a questionnaire with appropriate readability, reliability and proven discriminatory ability. *Full validity testing is continuing, and further versions of the FMPI may well take place in the future.*

Instructions:

1. The following instructions should be read to owners by the operator each time the FMPI is administered:
"This questionnaire asks you questions about your cat's ability to do various activities compared to what you think a normal adult cat without mobility impairment would be able to do.
Please read the questions carefully and place an 'X' in the appropriate box.
'Normal' is located here, and then there are various degrees of 'abnormal'. If the activity does not apply, such as if you do not have stairs in your home, check this box on the far right. Owners should be encouraged to answer all questions at every evaluation, and only select 'Not applicable' if the question or activity truly does not apply for their cat.

2. Upon completion of the questionnaire, the owner should return the questionnaire to the operator.

3. FMPI scores are calculated by assigning whole integer scores from 0 to 4, with 0 representing 'not at all', and 4 representing 'normal'.

4. The total FMPI score is the sum of scores for each question. Higher totals indicate less impairment with a possible range of (0-68). For analysis, total score or percent possible can be used. Calculation of percent possible is performed by taking the total score for the cat and dividing by the total possible points (the number of questions answered multiplied by 4).

FMPI%poss Score Q1-17 = (sum of Q1-17 scores) / (number of questions answered*4)

5. If repeat FMPI scores are acquired from an individual owner, they should not see their previous scores or responses prior to completing the questionnaire.

We welcome feedback on the FMPI. Please contact Dr. Duncan Lascelles using:
Duncan_Lascelles@ncsu.edu
The Comparative Pain Research Laboratory is very grateful to Morris Animal Foundation, Novartis Animal Health, and Boehringer Ingelheim Vetmedica Inc. for sponsoring the work that has led to the development and validation of the FMPI.

 Version 10

NC STATE
Veterinary Medicine
Comparative Pain
Research Laboratory

NAME: DATE:

FELINE MUSCULOSKELETAL PAIN INDEX

Please take some time to complete the following questions.

Please mark the circle that best describes your cat's ability to perform the following activities as compared to what you think a normal adult cat, without mobility impairment, would be able to do.

1. Walk and/or move easily?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

2. Run?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

3. Jump up (how well and how easily)?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

4. Jump up to kitchen-counter height in one try?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

Version 10

Please rate your cat's ability to:

5. Jump down (how well and how easily)?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

6. Climb up stairs or steps?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

7. Go down stairs or steps?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

8. Play with toys and/or chase objects?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

9. Play and interact with other pets?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

 Version 10

Please rate your cat's ability to:

10. Get up from a resting position?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

11. Lie and/or sit down?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

12. Stretch?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

13. Groom himself or herself?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

14. Interact with you and family members?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

Version 10

Please rate your cat's ability to:

15. Tolerate being touched and/or held?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

16. Eat?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

17. Use the litter box (get in and out, squat, cover waste?						
○	○	○	○	○		○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all		Not applicable

APPENDIX B SUMMARY OF ACTIVITY MONITORS AND RELEVANT LITERATURE

Summary of Activity Monitors and Relevant Literature in Cats

Device Name	Validation Studies	Other Studies
Actical	Measure of activity and distance moved in healthy cats and in cats with DJD (Lascelles et al., 2007c, Lascelles et al., 2008a) Differentiation between healthy cats and cats with DJD (Guillot et al., 2012)	<u>Activity levels</u> • Physical activity of overweight cats (de Godoy and Shoveller, 2017) • Physical activity using a running wheel (Detweiler et al., 2017) • Physical activity of cats with DJD (Gruen et al., 2017a) <u>Validation of CMIs</u> • FMPI and CSOM (Gruen et al., 2015) • MiCAT(C) (Klinck et al., 2018a) <u>Effect of therapeutic interventions on activity levels</u> • Meloxicam (Gruen et al., 2014, Guillot et al., 2013) • Robenacoxib (Adrian et al., 2019) • Gabapentin (Guedes et al., 2018b) • Tramadol (Guedes et al., 2018a) • antiNGF (Gruen et al., 2016) • Therapeutic DJD diet (Lascelles et al., 2010a) • 17β-estradiol (Wara et al., 2015) <u>Food intake</u> • Effect of photoperiod on (Kappen et al., 2014) <u>Diet and activity levels</u> • Effect of feeding method (Naik et al., 2018), frequency (de Godoy et al., 2015, Deng et al., 2011, Deng et al., 2014) and dietary content (Gooding et al., 2015, Gooding et al., 2016, Hooper et al., 2018, Thomas et al., 2017)

ActiWatch mini	No validation studies published.	<u>Activity levels</u> • Effect of housing conditions and human presence (Piccione et al., 2014, Piccione et al., 2013) <u>Therapeutic interventions</u> • Meloxicam (Monteiro et al., 2016) • Tramadol (Monteiro et al., 2017) <u>Validation of CMIs</u> • MiCAT(V) (Klinck et al., 2018b)

Clinical Metrology Instrument (CMI); Client-specific Outcome Measures (CSOM); Degenerative Joint Disease (DJD); Feline Musculoskeletal Pain Index (FMPI)

Summary of Activity Monitors and Relevant Literature in Dogs

Device Name	Validation Studies	Other Studies
Actical	Activity levels and distance moved (Hansen et al., 2007)	• Association of activity levels with signalment (Michel and Brown, 2014) • Influence of device attachment on activity levels (Martin et al., 2017) <u>Interventions</u> • Cartrophen (Brown et al., 2010) • Meloxicam (Muller et al., 2018) • Therapeutic DJD diet (Rialland et al., 2013)
Actigraph wGT3X+	Subjective direct observation and correlation with activity levels (Yam et al., 2011) Activity levels compared against	• Assessing activity levels during weight loss (Morrison et al., 2018, Morrison et al., 2014) • Assess stress levels in shelter dogs (Jones et al., 2014) • Evaluation of open source method for calculating physical activity (Westgarth and Ladha, 2017) • Assess activity levels during chemotherapy (Helm et al., 2016)

	Actical (Belda et al., 2018)	
Actigraph wGT3X-BT and GT9X	No validation studies published.	Combining Actigraph GT9X and PetPace data to measure activity (Ortmeyer et al., 2018)
Heyrex	Activity levels compared against Actical (Mejia et al., 2019)	Effect of environmental noise and music on dexmedetomidine-induced sedation (Albright et al., 2017)
PetDialog	Recognition of eight behavioural states (den Uijl et al., 2017)	
PetPace	Activity levels compared against Actical (Belda et al., 2018)	Combining Actigraph GT9X and PetPace data to measure activity (Ortmeyer et al., 2018)
Vetrax	Quantification of pruritic behaviours (Griffies et al., 2018)	Evaluation of changes in pruritic behaviours (Wernimont et al., 2018)
VetSens	No validation studies published.	• Predicting rest (Ladha and Hoffman, 2018) • Evaluation of open source method for calculating physical activity (Westgarth and Ladha, 2017) • Measuring canine gait (Ladha et al., 2017)
Whistle	Activity levels compared against Actical (Yashari et al., 2015)	• Activity recognition (Kiyohara et al., 2015)

Degenerative Joint Disease (DJD)

APPENDIX C BRISTOL CAT STUDY QUESTIONNAIRE

Questionnaire 8: My 6 year old cat

Thank you for taking the time to update us about your cat's progress, now that he/she is 6 years old.

As before, this questionnaire contains a mixture of new questions, as well as some questions that you have answered previously – so that we can see what, if anything, has changed for your cat.

Completing this questionnaire should be straightforward and take about 20 minutes. If there are any questions which you do not wish to answer, please leave them blank and move to the next question.

Please return your completed questionnaire in the envelope enclosed.

Thank you for your help – information about the "Bristol Cats" and early results from the study will be available from our website.

www.bristol.ac.uk/vetscience/cats

FREEPOST RSHR-AGRJ-UABZ
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University of Bristol
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Langford
BRISTOL
BS40 5DU
Tel/text: 07827 981412
Cat-study@bristol.ac.uk

SECTION A: Your cat's household

A1 Do you still have this cat?

	Tick one box
Yes	
No	

If "Yes", please go to question A4

A2 Why do you no longer have this cat?

Reason:

A3 Approximately how old was your cat when he/she left your household)?

Age of cat: .....

We are sorry to learn that you no longer have your cat. Please proceed to Section H to fill in your personal details.

If you would like to remain on our mailing list for newsletters please tick this box. ☐
Thank you for participating in this study.

A4 How happy do you think your cat is?

	Tick one box
Very happy	
Quite happy	
Not very happy	
Not at all happy	
I don't know	

A5 What factors contributed towards your answer above?

A6 How many cats in total (including your 'Bristol cat(s)') currently live in this household?

.....

A7

How frequently is this cat in a room where people smoke?	*Tick one box*
Never (currently and previously)	
Never (currently), but was previously (e.g. household member has stopped smoking)	
Less than once a week	
Once a week or more often	

A8 Please indicate whether or not your cat has spent time during the last week in these types of places ***inside*** your home:

	Tick one box per row			
	Not available to my cat	Available to my cat		
		Used by cat	Not used by cat	Don't know if used by cat
A 'hiding' place that you have created for your cat (e.g. a 'pyramid' bed or cardboard box)				
On a platform / ledge / raised area that your cat has previously used (but you didn't specifically create for your cat, e.g. on top of boiler, on windowsill)				
On a platform / ledge / raised area that you have provided for your cat (e.g. a cat climbing frame bought from a shop)				

A9 Please indicate whether or not your cat has spent time during the last week in the following activities ***inside*** your home:

	Tick one box per row			
	Not available to my cat	Available to my cat		
		Used by cat	Not used by cat	Don't know if used by cat
Using a scratching post that you have provided for your cat				
Using something else (other than a purpose built cat scratching post) to scratch on				
Playing with bought or home-made cat toys				
Playing with objects (not designed as a toy!) that the cat finds (e.g. a leaf)				

SECTION B: About your cat's activity levels and indoor/outdoor lifestyle

B1 How often, if at all, do you believe that your cat
a) hunts outside for prey ?
b) eats prey that he/she has caught?

	Tick one box per row				
	Most days	Quite often (1-2 times/week)	Not very often (1-3 times/month)	Never	Don't know
Hunts outside for prey					
Eats prey that he/she has caught					

B2 Which of these statements best describes your cat's indoor/outdoor access?

	Tick one box
Inside only – cat is not allowed outside	
Inside only – cat only goes out into enclosed 'run' or on a lead	
Inside and outside	
Outside only – cat is not allowed in the house	

If 'inside only', please go to section C.
If 'inside and outside', please continue with question B3.
If 'outside only', please go to question B4.

B3 Which of these statements best describes how much time your cat currently spends outside, **when he/she has unrestricted access to the outside?**

	Tick one box
He/she hardly ever spends time outside	
He/she spends a little time outside, but most of his/her time is spent inside	
He/she spends roughly equal amounts of time inside and outside	
He/she spends a little time inside, but most of his/her time is spent outside	
He/she hardly ever spends time inside	

B4 To what extent does your cat have access to outdoor space beyond your garden?

	Tick one box
Restricted at all times by a lead	
Restricted to the garden by a "cat proof" fence	
No restrictions	
Other *(please specify)*: ……	

SECTION C: About your cat's diet

Many of these questions will be familiar as we would like to find out about any changes in your cat's diet, appetite and food preferences.

C1 Which of the following sources of water do you know, or think, that your 'Bristol cat' drinks from?

	Tick all that apply
Bowl of unfiltered tap water	
Bowl of filtered tap water	
Bowl of mineral water	
Cat drinking fountain – filtered tap water	
Cat drinking fountain – unfiltered tap water	
Toilet	
Running tap	
Outside source (stream, pond, puddles, etc)	

C2 How much do you feed your cat the following types of food?

	Tick one box per row				
	Only food in diet	*Major part (half or more) of daily diet*	*Minor part (less than half) of daily diet*	*Only feed occasionally*	*Never feed*
Commercial wet **adult** cat food (e.g. tins, pouches, foil packs)					
Commercial **adult** dry food (e.g. biscuits, kibbles)					
Uncooked/raw fresh food (e.g. fish, chicken)					
Cooked fresh food (e.g. fish, chicken)					
Cow's milk/cream					
Cat milk					

C3	Now, using the label on your cat's commercial wet food (e.g. tins, pouches, foil packs), please estimate which of these phrases best describes the total weight of commercial wet food that you think your cat eats each day.

	Tick one box
None	
100g (e.g. one pouch or quarter of a standard-sized tin)	
150g (e.g. one and a half pouches, or just over a third of a standard-sized tin)	
200g (e.g. two pouches or half a standard-sized tin)	
250g (e.g. two and a half pouches, or nearly two-thirds of a standard-sized tin)	
300g (e.g. three pouches, or three-quarters of a standard-sized tin)	
Other *(please specify):*	

C4	Please can you estimate (preferably using your kitchen scales) the weight (in grams) of dry food (e.g. biscuits, kibbles) that you think your cat eats each day, and enter this amount below. *(If your cat does not have dry food, please enter "0".)*

.....grams

Is this an accurate or estimated weight?

Accurate	
Estimate	

C5	If your cat receives home-prepared food (e.g. fresh fish), please describe what you would typically feed per day: Please include information on the type (i.e. cut of meat, fish), preparation method and amount.

C6	If you feed your cat commercial cat food and you mainly feed one or two brands (e.g Whiskas Tasty Textures / Felix Sensations etc, dry or tinned), what brands and varieties are they?

Brand: Variety:
Brand: Variety:

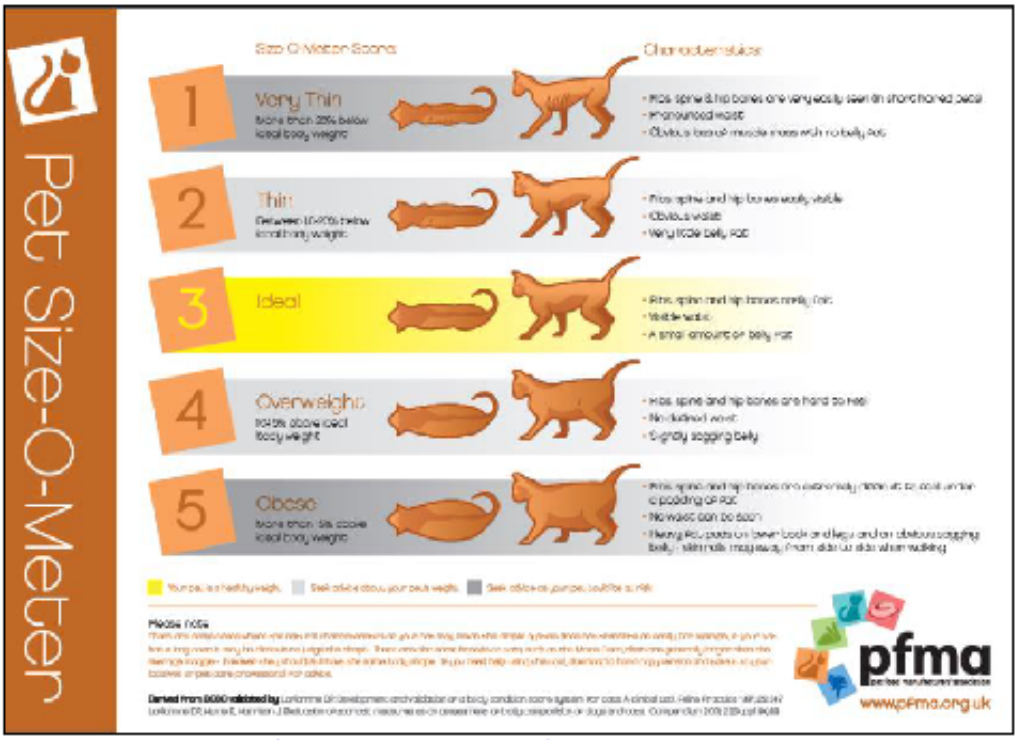
C7 If you use 'wet food', which of the following do you usually feed?

	Tick all that apply
N/A, do not feed wet food	
Tins	
Pouches/sachets	
It varies	
Meat/fish in gravy	
Meat/fish in jelly	
Meat/fish pate	
Meat/fish Supermeat / Meaty Loaf	
Other (please specify):	

C8 Using the following instructions, please assess the body condition of your 'Bristol Cat' and indicate the body condition score below:

To work out your cat's individual body condition score, you need to do three checks:

1. Rib Check: Run both your hands, palms facedown across your cat's ribcage on either side
2. Profile Check: View your standing cat from a side-on angle, this is best done if you are level with your pet
3. Overhead Check: Look down at your standing cat from an overhead angle



Source: www.pfma.org.uk/_assets/images/general/file/PFMA%20Cat%20PSOM%20Final%20Web%20Version%20070809.pdf

Body condition score of 'Bristol Cat': .....

SECTION D: About your cat's health and veterinary contact

D1 Has your cat visited a veterinary practice during the last ***12 months***?

	Tick one box
Yes	
No	

If 'No', go to D5.

D2 What was the purpose of this visit / these visits?

	Tick all that apply
Routine general health check	
Slimming club / weight watchers clinic	
Dental check	
Behavioural advice	
Vaccination	
Microchipping	
Neutering	
Flea prevention	
To treat fleas	
Worm prevention	
To treat worms	
Abscess / cat bite	
Attacked by dog	
Cat flu	
Coughing / wheezing	
Ear problem (e.g. ear mites)	
Urinary problem (e.g. cystitis, blocked bladder)	
Skin problem (e.g. itchy, excessive grooming, hair loss)	
Eye problem (e.g. conjunctivitis)	
Dental / tooth / mouth problem	
Lameness / limb problem, including broken or dislocated bone	
Checking / investigating heart problem (e.g. murmur)	
Vomiting / sickness	
Diarrhoea	
Cat 'off colour'	
Reduced appetite	
Increased appetite	
Increased thirst	
Weight loss	
Other *(please give full details):*	

D3	Please use this space to provide further details of problems that have led to veterinary visits indicated above. If a vet has made a diagnosis please include this information.
D4	Has your cat had any of the following diagnosed by a vet?

	Tick all that apply
Hyperthyroidism	
Heart disease	
Renal failure	
Diabetes	
Cancer	
None of these	

D5	Please provide details of any medication (excluding routine flea/worming treatment) that your cat has received during the last 12 months. Information we are interested in includes: name of medication, dose, frequency medication given, date started, date finished (or length of course).

D6 During the ***last 12 months,*** has your cat had any of the following illnesses/injuries/conditions which you felt were not serious enough to seek veterinary attention for?

	Tick one box per row		
	Yes	*No*	*Not sure*
Fleas			
Worms			
Abscess / cat bite			
Attacked by dog			
Cat flu			
Coughing / wheezing			
Scratching his/her ears and/or shaking his/her head			
Urinary problem (e.g. cystitis, blocked bladder)			
Skin problem (e.g. itchy, excessive grooming, hair loss)			
Eye problem (e.g. conjunctivitis)			
Dental / tooth / mouth problem			
Lameness / limb problem			
Heart problem (e.g. previously detected murmur)			
Vomiting/sickness			
Diarrhoea			
Cat 'off colour'			
Reduced appetite			
Increased appetite			
Increased thirst			
Weight loss			
Other *(please specify)*:			

D7 Please use this space to provide further details of problems that your cat has had but which have not led to veterinary attention, as indicated above.

D8 During the ***last 12 months***, have you seen any worms, fleas / flea dirt or signs suggestive of worms or fleas (e.g. scratching, worms in vomit or faeces)?

	Tick one box per row		
	Yes	*No*	*Not sure*
Evidence of worms			
Evidence of fleas			

D9 How many times, if at all, have you wormed or used flea treatment/prevention on your cat during the last 12 months?

	Tick one box per row			
	Never	*Once or twice*	*Three or more times*	*Don't know*
Wormer				
Flea treatment				

D10 Is your cat insured?

	Tick one box	
	Yes	*No*
Insured		

D11 Please indicate the date of your cat's last vaccination. *(If not sure, please enter approximate month and year in space below)*:

Date of last vaccination...../...../.....

Or, approximate date:.....(month) .....(year)

☐ Not applicable: never been vaccinated **(go to D15)**

D12 Was your cat vaccinated at the practice that was your 'usual' veterinary practice at that time?

	Tick one box
Yes – usual veterinary practice (please also tick if you are a vet and usually vaccinate your own cat)	
No – I went to a different practice on this occasion	

D13 Are the details of your cat's most recent vaccination recorded on his/her vaccination card?

	Tick one box
Yes	
No	
Can't remember	

D14 At the last vaccination, which of the following diseases did your vet recommend your cat was vaccinated against and which diseases was your cat actually vaccinated against?

	Tick all that apply					
	Vet recommended			*Cat vaccinated against*		
Disease	*Yes*	*No*	*Not sure*	*Yes*	*No*	*Not sure*
Bordetella						
Cat flu (Feline Herpes Virus (FHV-1) / Feline Calicivirus (FCV))						
Feline Infectious Enteritis (FIE) or Panleucopenia						
Feline Leukaemia Virus (FeLV)						
Feline Chlamydophilosis						
Rabies						

D15 Excluding emergency/out of hours appointments, do you use different veterinary practices for different problems/treatments for this cat, or do you use the same veterinary practice for everything?

	Tick one box
Same practice for everything	
Different practices for different problems/illnesses/treatments	
Prefer not to answer this question	
Other *(please specify)*:	

D16 Is your 'Bristol cat' neutered (desexed)?

	Tick one box
Yes – at or before 5 years of age	
Yes – since 5 years of age	
No	

D17 How frequently, if at all, do you do the following to help keep your cat's teeth and mouth healthy?

	Tick one box per row				
	Every day	*A few times a week*	*Once a week*	*Less frequently*	*Never*
Brush teeth					
Use dental gel or mouth rinse					
Use food or water additive					
Feed dental treats					
Feed a special dental health diet					
Feed home-prepared fresh food					
Other *(please specify)*:					

D18 If you use any 'dental health' products mentioned in the question above, please name the product(s) used:

D19 During the last 12 months, has a vet/vet nurse commented on the health of your cat's teeth and mouth?

	Please tick the comment that applies best
Yes – advised that teeth and mouth are in good health	
Yes – advised that cat has some dental/oral disease and that dental treatment (under anaesthetic) may be necessary in the future	
Yes – advised that that cat has a 'scale and polish' (under anaesthetic)	
Yes – advised that cat has dental/oral disease and recommended that dental treatment under anaesthetic (excluding a 'scale and polish only') was needed	
No – no comment on teeth/mouth made	
N/A – has not seen a vet or vet nurse in the past 12 months	

D20 Has your cat had any dental work carried out during the last 12 months by the vet?

	Tick one box
Yes	
No	

If 'no', please go to question D22.

D21

If your cat has had dental work carried out during the last 12 months, please provide further information below regarding the work carried out:	*Tick one box*
Scale and polish only	
A few teeth extracted (e.g. 1 or 2)	
A moderate number of teeth extracted (e.g. 3-6)	
A lot of teeth extracted (e.g. 7 or more)	
Other (please specify, including reasons for extractions, if known:)	

D22 During the last 12 months, have you seen your cat drinking, urinating or defecating?

	Tick one box for each row	
	Yes	*No*
Drinking		
Urinating		
Defecating		

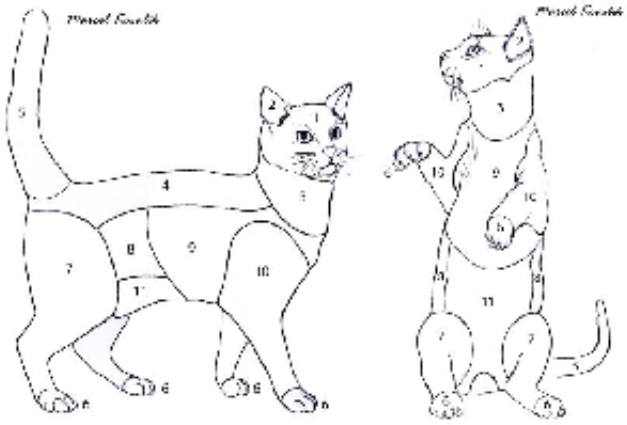
D23 Please indicate whether you are aware of any changes in your cat in the areas of drinking and urination, during the last 12 months.

	Tick one box for each row			
	Not aware of any changes	No change	Increased	Decreased
Amount of water that cat drinks				
Amount of urine that cat passes				

D24	If you think that your cat has been drinking more, or less, water during the last 12 months, please indicate the reason(s) for your answer.	
		Tick all that apply
	Water bowl needs refilling more/less frequently	
	I see the cat drinking inside more/less often	
	I see the cat drinking outside more/less often	
	Other *(please specify)*	

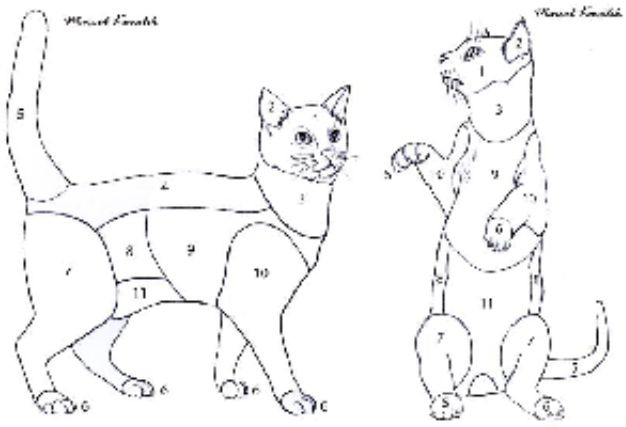
D25	Which, if any, of the following have you been aware of whilst watching your cat urinating?			
		Tick one box for each row		
		Yes	*No*	*N/A have not seen cat urinating*
	He/she strains or appears to have difficulty urinating			
	He/she has passed blood when urinating			
	He/she vocalises (e.g. miaows) before or during urination			
	He/she sometimes urinates in different locations (around the house and/or outside)			

D26 Using the diagrams below, please indicate how frequently during the last week, if at all, has your cat been grooming, scratching, biting, licking, chewing, nibbling, rubbing (out of discomfort rather than 'normal rubbing or grooming behaviour') him/herself in <u>any area</u> within each of these marked regions.



	Tick one box for each row				
	Almost continuously	A lot of the time and/or for long spells of time (including when eating, playing or being distracted)	A moderate amount of time (but not when eating, playing or being distracted)	Only occasionally (and out of discomfort rather than 'normal rubbing or grooming behaviour')	Not at all (out of discomfort rather than 'normal rubbing or grooming behaviour')
1 (head)					
2 (ears)					
3 (neck)					
4 (back and base of tail)					
5 (tail)					
6 (paws)					
7 (back legs and thigh, excluding paws)					
8 (flank)					
9 (chest and sides)					
10 (front legs and shoulders, excluding paws)					
11 (tummy)					

D27 Using the same two diagrams, please indicate which of the following list, if any, you have noticed on your cat:



	Tick all that apply one box						
	Bald patches / clumps of hair missing / falling out	General thinning of the coat (including short barbered hair but excluding usual moulting)	Scabs / crusts	Lumps / bumps / swellings	Redness of the skin	Bleeding	None of these - hair and skin appear normal
1 (head)							
2 (ears)							
3 (neck)							
4 (back and base of tail)							
5 (tail)							
6 (paws)							
7 (back legs and thigh, excluding paws)							
8 (flank)							
9 (chest and sides)							
10 (front legs and shoulders, excluding paws)							
11 (tummy)							

SECTION E: What is normal for your cat at the moment?

E1 During a 'typical' week, which of these phrases best describes the ***usual*** consistency of your cat's faeces?

	Tick one box
Have not seen faeces	
Dry/hard	
Firm	
Soft/loose	
Runny/watery	
Varies	

E2 Please select the statement that best applies to your cat for each of these activities.

	Tick one box per row			
My cat....	No	Maybe	Yes	N/A
is less willing to jump up or down than he/she was 18 months ago				
will only jump up or down from lower heights				
shows signs of being stiff at times				
is less agile than he/she was 18 months ago				
shows signs of lameness or limping				
has difficulty getting in or out of the cat flap				
has difficulty going up or down stairs				
cries when picked up				
has accidents outside the litter tray				
spends less time grooming than he/she did 18 months ago				
is more reluctant to interact with me than he/she was 18 months ago				
plays less (e.g. with other animals and/or toys) than he/she did 18 months ago				
sleeps more and/or is less active than he/she did 18 months ago				
cries out loudly for no apparent reason				
appears forgetful or disorientated				

E3 Please rate how well you think your cat is able to carry out the following activities during a 'typical' week?

	Tick one box per row			
	Very well	Well	Adequately	Not well
Grooming				
Eating				
Moving around				

E4 Please indicate how easily your cat can jump up onto the following places:

	Tick one box per row					
	Very easily	Quite easily	Not very easily	With a lot of difficulty	Cannot	Don't know
Sofa						
Your bed						
Kitchen work surface						
Kitchen / dining table						

We are assuming the following *approximate* standard heights.
Sofa: 40 cm (16") Work surface: 90 cm (36")
Bed: 55 cm (22") Table: 78 cm (31")

If your furniture is a 'non-standard' height, please provide a measurement at the end of the questionnaire in the space for further information.

E5 Please rate your perception of your cat's activity levels during the past week using the options below.

	Tick one box
Very active	
Quite active	
Not very active	
Not at all active	

E6 Do you believe that there are currently any 'external' factors that are affecting your cat's mental or physical wellbeing? (E.g. bullying from another cat, moving house).

	Tick one box
Yes	
No	

If 'No', go to E8.

E7 We would be grateful if you could provide further details about these 'external' factors.

E8 Please rate your perception of your cat's overall quality of life ***during the past week*** using the options below.

	Tick one box
Excellent	
Good	
Average	
Fair	
Poor	

E9 What factors contributed towards your selection of this rating?

F4 For each of the behaviours listed above, (or for the first three listed), please provide the following information:

Behaviour	*Tick all that apply*			
	Is this behaviour a problem to you?		Please indicate whether or not you have sought help for these behaviour problems	
	Yes	No	Yes	No
Behaviour 1				
Behaviour 2				
Behaviour 3				

If 'No' to all behaviours, please go to section G.

F5 Please tick which of these sources you have sought help from for each of these behaviour problems, (or for the first three listed).

	Tick all that apply		
	Behaviour 1	Behaviour 2	Behaviour 3
Vet			
Vet behaviourist			
Behaviourist			
Vet Nurse			
Other members of vet practice staff			
Friend			
Books			
Animal welfare organisation staff/online resources			
Online sources not mentioned above (including forums)			
Other *(please provide details)*			
Have not sought help			

SECTION G: Your cat's neighbourhood

G1 If your cat has been registered with a veterinary practice (for the first time, or with a different veterinary practice), since you completed the last questionnaire for the 'Bristol Cats' study, and you are happy for us to access your cat's veterinary records, please provide the **name and address** of your cat's new veterinary practice below:
Name of veterinary practice:
Address:

G2 Have you moved house within the last 12 months?

	Tick one box
Yes	
No	

If 'No', please go to G5.

G3 Which of these phrases best describes the location of your home?

	Tick one box
In a rural area	
In a village or suburban location	
In a town or city location	
Don't know	

G4 Do you have a garden? (Include communal gardens.)

	Tick one box
Yes	
No	

The next few questions check for the contact your cat has with local dogs and cats, possibly due to new dogs/cats moving to your area, or because you have moved house.

G5 How many dogs (from other households) do you know of that are in your immediate neighbourhood? (I.e. dogs that your cat might see and/or hear outside regularly.)

	Tick one box
None	
1-5	
6-10	
11 or more	

G6 How many cats (from other households) do you know of that are in your immediate neighbourhood? (I.e. cats from other household that your cat might see and/or hear outside regularly.)

	Tick one box
None	
1-5	
6-10	
11 or more	

If 'None', go to G12.

G7 Do any of these cats stare into your house through catflaps, doors or windows?

	Tick one box
Yes	
No	
Don't know	

G8 In which of these ways does your cat react if he/she sees any of these cats in his/her house or garden?

	Tick all that apply
Ignores them	
Stays still	
Hisses or spits	
Chases them	
Swipes his / her paw	
Runs away	
Rubs against them	
Licks or grooms them	
Plays with them	
Skirts around them	

If your cat is an 'indoor only' cat, please go to G12.

G9 How many cats (from other households) does your cat come into contact with at least once a week, in each of the following categories?

	Tick one box per row			
	None	*1-3*	*4 or more*	*Don't know*
'Friends' of my cat (e.g. they play, spend time together)				
'Acquaintances' of my cat (e.g. they meet occasionally but there is little contact between them)				
'Enemies' of my cat (e.g. they fight, one of them will chase the other, they avoid each other)				
Other *(please specify):*				

G10 Do any of these cats come into your house?

	Tick one box
Yes	
No	
Don't know	

G11 Do any of these cats come into your garden?

	Tick one box
Yes	
No	
Don't know	

G12 During the last six months, how often, if at all, do you think your cat has been involved in a fight with another cat?

	Tick one box per column	
	Cats within the household	*Cats from another household*
Not applicable (e.g. no other cats in household, cat does not have outside access)		
Never		
Once a month or less often		
2-4 times a month		
Once a week or more often		

G13 Please use this space to tell us about any ***major changes*** relating to your cat's **environment / behaviour / diet / health** that have taken place over the last 12 months and which have not been covered in this questionnaire.

G14 All things considered, how willing would you be to take on the life your cat is now living?

	Tick one box
Very willing	
Quite willing	
Not very willing	
Not at all willing	
I don't know	

G15 Please use this space for any additional comments you would like to add:

SECTION H: Final details

Finally, please complete the details below for our records. This final section is very important and enables us to link this questionnaire with others you have completed for your cat. Please be reassured that this information is strictly confidential and will be used for no other purposes. Your contact details will ONLY be used for the purposes of the 'Bristol Cats' study.

Date of questionnaire completion	
IDENTIFYING INFORMATION:	
Bristol Cat 'Owner ID'	
Bristol Cat 'Cat ID'	
Name of cat	
Your name	
Address	
Email address	
Contact telephone number	

Thank you very much for your time and help in completing this questionnaire.

We really appreciate the time that you have taken to complete this questionnaire to tell us about your cat. The information you give us about your cat will help us to help cats in the future. If you have any questions, please contact a member of the study team.

Signature: .....Date: .....
Please return your completed questionnaire in the envelope enclosed.
Freepost RSHR-AGRJ-UABZ
Bristol Cats: Dr Jane Murray
University of Bristol, Langford House, Langford, BRISTOL, BS40 5DU

APPENDIX D TRAUMA-RELATED KEYWORDS FOR FREE TEXT MINING

RTA	Vehicle	Break	Fell
Hit by	Ran	Broke	Fall
Road	Trauma	Fracture	Attack
Car	Injur*	Dislocat*	Bit*

Road traffic accident (RTA)

APPENDIX E STUDY ONE: BREED INFORMATION

Breed	N (%) of cats
DSH and their crossbreeds	537 (67.7%)
DLH and their crossbreeds	100 (12.6%)
British short hair	44 (5.5%)
Maine Coon	25 (3.2%)
Siamese	13 (1.6%)
Ragdoll	10 (1.3%)
Burmese	8 (1%)
Birman	7 (0.9%)
Korat	7 (0.9%)
Siberian	6 (0.8%)
Norwegian forest	5 (0.6%)
Oriental shorthair	4 (0.5%)
Devon Rex	3 (0.4%)
Persian	3 (0.4%)
Selkirk Rex	3 (0.4%)
Tonkinese	3 (0.4%)
Bengal	2 (0.3%)
Burmilla	2 (0.3%)
Havana	2 (0.3%)
Ragamuffin	2 (0.3%)
Exotic Shorthair	2 (0.3%)
Scottish Fold	1 (0.1%)
Singapura	1 (0.1%)
Malayan	1 (0.1%)
Russian Blue	1 (0.1%)
Somali	1 (0.1%)

APPENDIX F RECRUITMENT E-MAILS AND ADVERTISEMENTS

RECRUITMENT E-MAIL FOR BC STUDY PARTICIPANTS

Hello from the Bristol Cats Study & the Feline Activity Study!

I'm very excited to inform you that your cat, already a proud participant of the Bristol Cat study, is also eligible to participate in the in the **Feline Activity Study** which investigates the activity levels of our feline friends using cat "FitBits"!

As your cat's welfare is our top priority, included cats should also:

- Be happy to meet and be stroked by strangers.
- Be happy to wear a breakaway (safety) collar – do not worry if your cat is not wearing one already, this can be provided along with step by step instructions of how to slowly introduce your cat to it written by feline specialists.

What is required from you – and your cat?

- Completion of two short questionnaires (~15 minutes total).
- A 30-60-minute home visit to meet both of you and conduct a gentle examination of your cat's joints.
- Your cat wearing a light activity monitor on their collar for 2 weeks.

Please do not hesitate to contact me if you have any questions, I am looking forward to your response and I hope you will consider participating in this fantastic study!

If not, please accept my deepest thanks for your ongoing participation in the Bristol Cats study!

Best wishes,

RECRUITMENT LETTER FOR BC STUDY PARTICIPANTS

Dear <owner name>,

A huge thank you for your continued participation in the Bristol Cats study!

As part of the Bristol Cats study, we sometimes undertake more in-depth studies and, in order to really explore specific issues, we ask some of our Bristol Cat Owners to have greater involvement, such as chatting to us in more detail about your cats, or even allowing us to meet them in person!

We contacted you earlier this month to invite you to participate with <cat's name> in one such study, looking at activity levels in cats. Helping us with this study would involve Evelyn Maniaki, our feline scholar, visiting you at home to find out a bit more about what [cat name] likes to get up to, gently examine <his/her> joints and place a cat "FitBit" on <him/her>. If <insert cat's name here> does not normally wear a collar that is fine; you can still enrol.

If you and <insert cat's name> might be interested in helping us, please simply reply to this email with 'yes please I'd like to find out more about what would be involved' and we will get in touch with more details! If for any reason you do not feel that this study is for you, that is absolutely fine.

Once again, thank you for your years of participation, as we are hugely grateful for each cat and each owner's input. I hope that you have a wonderful Christmas with your cat(s)!

Best Wishes,

RECRUITMENT ADVERTISEMENT FOR NON-BC STUDY PARTICIPANTS

Feline Activity Study

If your cat…

- **Is over 6 years of age,**
- **Is kept indoors (or has outdoors access within a closed run and/or on a lead),**
- **Isn't on any pain medication, and**
- **Lives within 1-2 hours' drive from Bristol or Bournemouth**

Then you are invited to participate in our study which investigates the activity levels of our feline friends using cat "FitBits"!

We are using activity monitors to study the effect of joint disease on feline activity levels and hope this study can further advance our understanding of this challenging and painful condition.

As your cat's welfare is our top priority, included cats should also:

- Be happy to meet and be stroked by strangers.
- Be happy to wear a breakaway (safety) collar – don't worry if your cat isn't wearing one already, this can be provided along with step by step instructions of how to slowly introduce your cat to it.

What is required from you – and your cat?

- Completion of two short questionnaires (~15 minutes total).
- A 30-60-minute home visit to meet both of you and conduct a gentle examination of your cat's joints.
- Your cat wearing a light activity monitor on their collar for 2 weeks.

Contacts:

For more information or to get in touch with Evelyn Maniaki at Bristol Veterinary School, visit our Facebook page @feline.activity.study, e-mail cat-study@bristol.ac.uk or call 07827 981412.

Even if you are unable to participate directly in this study, you can still help by spreading the word about it!

Langford Vets

University of BRISTOL

APPENDIX G COLLAR HABITUATION INSTRUCTIONS

University of BRISTOL

COLLAR INTRODUCTION GUIDELINES

Many thanks for agreeing to help us with our study where your cat will wear a collar with the attached accelerometer for approximately 2 weeks, allowing us to assess their activity. Your cat's welfare is our top priority and, as your cat does not normally wear a collar, we have written these guidelines to help you introduce it gradually.

- The collar you have been provided with is a breakaway (safety) collar. This means that it will release if your cat gets caught on anything within the house.
- By giving your cat opportunities to do things they enjoy whilst wearing the collar, positive associations will be built up which will ensure your cat feels relaxed and happy whilst wearing it. This can be achieved, for example, by giving your cat tasty treats or playing with their favourite toy whilst the collar is being worn.
- The speed that you progress through the steps will depend on your cat and, as every cat is different, this process may take anything from a couple of days to a week. Once you are confident that your cat is relaxed, you can progress to the next step. However, if your cat shows any signs of being worried (see later), you should go back to the step in which your cat showed signs of relaxation. If at any point during the collar introduction you have any concerns, please do not hesitate to contact us.
- Cats tend to choose the "flight" rather than the "fight" approach when confronted with something they are worried about, so if your cat freezes or moves away when you approach with the collar, that is your cat's way of telling you that they are worried.
- Carrying out the collar introduction process in an area that allows your cat to walk off or hide if they want will help them feel safer and more comfortable.

Feel free to replace feeding in the following steps with any other activity your cat enjoys and can therefore be used to build up positive associations:

1. Whilst holding the cat collar in obvious view or resting it on your lap if your cat is very timid, encourage your cat to approach you. If your cat approaches in a relaxed way, wait until they are close to you then give them a small amount of food. If your cat is slightly hesitant, do not wait until your cat has come all the way to you but, instead, *gently* throw some food towards them when they move in your direction. Do not move on to the next stage unless you are confident that your cat is approaching you in a relaxed way. Continue to feed when your cat is close to you and whilst holding the collar.
2. Hold the collar out to allow your cat to sniff it, giving them some food for showing interest in it. Repeat this several times, so that you can be 100% certain that your cat is relaxed in the presence of the collar.
3. Hold the collar a little bit away from your cat and fasten it whilst giving them some food, noting how they react to the 'click' noise it makes when it fastens. If your cat is worried by the 'click', repeat starting further away, far enough that your cat is not worried. Continue by gradually decreasing the distance between the collar and your cat until you can fasten and unfasten it very close without your cat showing any signs of worry.

4. Whilst feeding your cat, gently place the collar around their neck but do not fasten it, simply rest it around their neck for a couple of seconds. Repeat until your cat is relaxed with you placing the collar around their neck.
5. Repeat the previous step, but this time fasten and then immediately unfasten the collar. Repeat until your cat is relaxed having the collar fastened and unfastened.
   Gradually increase the amount of time your cat wears the collar for. If your cat appears relaxed once the collar is on, you will be able to increase the amount of time your cat wears the collar for relatively quickly, whilst ensuring your cat continues building positive associations with it. Occasional scratching at the collar is OK, but if your cat looks worried or irritated you may need to build up the time your cat spends wearing the collar more gradually.

<u>Monitoring your cat's response to the collar</u>

It is important that you monitor your cat as you introduce them to the collar and that you only progress on to the next step of training when you are 100% certain your cat is happy with the previous step. Cats use their body language to tell us how they feel and if you notice any of the key signs outlined below, you should move a step back and take it from there.

- **Avoidance:** Your cat may walk (or run!) away or hide, either when you approach or when you attempt to put the collar on.
- **Eating:** Your cat may stop eating or refuse to take the food offered, despite them not being full and the food being something that they would normally eat immediately.
- **Changes in body posture and/or facial expression:** A relaxed cat will have a 'soft' body posture, possibly with paws tucked underneath if sat down or with a raised tail when approaching you. Signs of worry could be:
    - a cat that is tensing up, with or without an arched back, moving away from you or freezing in place
    - a cat with its hairs on end, most commonly on the base of the tail
    - a cat with a 'tucked' tail wrapped closely around their body which may or may not be swishing
    - a cat with ears in a fixed, backwards position or completely flattened
    - a cat with big, dilated pupils

APPENDIX H ONLINE INCLUSION QUESTIONNAIRE

Feline Activity Study

Page 1: Feline Activity Study - Inclusion Criteria

Thank you for your interest in our study.

If your cat ....

- **Is over 6 years of age,**
- **Is kept indoors (or has outdoors access within a closed run and/or on a lead),**
- **Isn't on any pain medication, and**
- **Lives within 1 hours' drive from Bristol or Bournemouth**

Then you are invited to participate in our study which investigates the activity levels of our feline friends using cat "FitBits"! 🐱

Completing the questionnaire should be straightforward and take about 5 minutes.

Please let us know if you have any questions before or during completing this questionnaire.

Basic information about you and your cat

E-mail address * *Required*

What is the first part of your postcode? * *Required*

1 / 7

Your name * *Required*

Your cat's name *Optional*

How old is your cat? (in years)

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

(dd/mm/yyyy)

What is your cat's breed?

What is your cat's gender?

- Male
- Female

Is your cat neutered (desexed)?

- Yes
- No

Does your cat have outside access, excluding going out into an enclosed 'run' or on a lead?

- Yes
- No

Please use this space to provide further details of your cat's outdoor access, if applicable.

During the last 12 months, has your cat had any problems that have led to veterinary visits?

- Yes
- No

Please use this space to provide further details of problems that have led to veterinary visits. If a vet has made a diagnosis, please include this information.

During the last 12 months, has your cat had any problems which you felt were not serious enough to seek veterinary attention for?

- Yes
- No

Please use this space to provide further details of problems that you felt were not serious enough to seek veterinary attention for.

Is your cat on any medication or supplements, excluding routine flea/worming treatment?

- Yes
- No

Please provide details of any medication or supplements, excluding flea/worming treatment, that your cat is receiving / has received over the last 6 months. This should include name of medication, dose, frequency administration and date started/finished (or course length).

Does your cat already wear a collar? (if not we can help to gradually get him/her used to wearing the activity monitor)

- Yes

- No

Page 2: Your cat's mobility

	Please choose the answer that best applies to your cat for each of the following statements. My cat...			
	Yes	Maybe	No	Not applicable
1. ...is less willing to jump up or down than he/she was 18 months ago.	○	○	○	○
2. ...will only jump up or down from lower heights.	○	○	○	○
3. ...shows signs of being stiff at times.	○	○	○	○
4. ...is less agile than he/she was 18 months ago.	○	○	○	○
5. ...shows signs of lameness or limping.	○	○	○	○
6. ...has difficulty going up or down stairs.	○	○	○	○
7. ...cries when picked up.	○	○	○	○
8. ...has accidents outside the litter tray.	○	○	○	○
9. ...spends less time grooming than he/she did 18 months ago.	○	○	○	○
10. ...is more reluctant to interact with me than he/she did 18 months ago.	○	○	○	○
11. ...plays less (e.g. with other animals and/or toys) than he/she did 18 months ago.	○	○	○	○
12. ...sleeps more and/or is less active than he/she did 18 months ago.	○	○	○	○

Page 3: Thank you very much for your help!

Thank you very much for completing this initial questionnaire!

We really appreciate the time that you have taken to complete this questionnaire to tell us about your cat. We will be contacting you in the next few weeks to let you know if you are eligible for this study.

If you have any questions, please contact Dr Evelyn Maniaki by:

e-mail: cat-study@bristol.ac.uk

phone: 07827 981412

post: Bristol cats (FREEPOST RSHR-AGRJ-UABZ) Dr Emily Blackwell, University of Bristol, Langford House, Langford, North Somerset, BS40 5DU

https://www.facebook.com/feline.activity.study/

APPENDIX I STUDY PARTICIPANT INFORMATION SHEET

University of BRISTOL

PARTICIPANT INFORMATION SHEET

Study title: The impact of feline degenerative joint disease on mobility and quality of life in cats

Research investigator: Dr Evelyn Maniaki

Supervisors: Dr Emily Blackwell; Dr Jo Murrell; Professor Sorrel Langley-Hobbs

We would like to invite you and your cat to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for both of you. Talk to others about the study if you wish. Please do not hesitate to ask us if there is anything that is not clear.

What is the purpose of the study?

Feline degenerative joint disease (DJD) is a common, but challenging condition in cats, with prevalence estimates ranging between 61% and 99% in cats and increasing with age. Whilst it is clear that DJD can lead to reduced mobility and pain, with significant potential impacts on the cat's quality of life (QoL), little is known about risk factors for this condition. Diagnosis of DJD is far from straightforward because it primarily depends upon owners detecting changes in the activity (e.g. reluctance to jump, reduced activity, sleeping more, stiff gait) or behaviour (e.g. sleeping more, playing less, grooming less, aggression towards owner or other cats) of their cat, then seeking veterinary advice. As cats are "masters of disguise", it is likely that a significant number of cats go undetected. Differences in activity between cats with DJD and normal cats have been detected using accelerometry (imagine a FitBit – but for cats!) and this new technology could also be useful in picking up early signs of DJD. Ultimately, early detection of DJD would allow a multimodal approach (e.g. environmental modification, physiotherapy) to delaying/halting progression of the disease by educating veterinary personnel and owners, thereby improving the cat's QoL.

Approximately 9% of UK pet cats are thought to live indoors. There are some obvious benefits to keeping cats indoors, primarily the avoidance of road traffic accidents, predation and reduced exposure to infectious disease, however concerns have been raised about an indoor cat's inability to display "normal" behaviours such as hunting, possibly resulting in an increased risk of problematic behaviours. This study will also investigate the complexity of the home environment and husbandry of indoor cats, comparing this information to owner-reported behaviours.

Why have I (and my cat!) been invited?

We are looking for cats over 6 years of age, of any breed, some of whom have early signs of DJD and others who do not. The cats should be otherwise healthy and not be on any medication, excluding flea/worm treatment and joint or other supplements. The cats should also not have outdoor access, unless that is limited on a lead or within a closed run.

Do I have to take part?
We would love you to help us, but it is entirely up to you to decide if you and your cat would like to join the study. We will describe the study and go through the process in this information sheet, but feel free to contact us if you have any questions. If you decide to help us, but then change your mind, you would be free to withdraw at any time, without giving a reason.

What will happen to me (and my cat!) if I take part and what will I (and my cat!) have to do?
This study will be conducted in your home. To participate in this study, your cat must not be fearful of meeting and being stroked by strangers. You also need to be happy for your cat to wear a breakaway (safety) cat collar with the attached accelerometer for a short period of time. If your cat has never worn a collar or not wearing a breakaway collar, one will be provided. Collar introduction will be a step by step process; we will provide you with instructions on how to do so and your cat will be given a minimum of seven days to acclimatise to wearing it. Visits will be scheduled for a mutually convenient date and time, with a start time between 8am and 7pm. Most visits will be scheduled on weekdays, but weekend dates will also be possible. Each participating owner will need a total of two visits. The initial visit will take 30-60 minutes, whilst the visit to remove the collar and accelerometer will be approximately 15 minutes.

Questionnaire completion
Before we pay you a visit, we will ask you to complete two short (~15 minutes total) questionnaires that will include questions about your cat's current health, mobility, behaviour, and quality of life.

What is required from my cat?
To prevent your cat being worried before, during and after the visits, Evelyn will allow your cat to acclimatise to her presence for at least 15 minutes before any handling and adhere to the principles of feline-friendly practice. This encompasses a long list of cat friendly rules, but for example Evelyn will allow the cat to approach her rather than the other way around, she will speak with a soft and calm voice and she will allow the cat to sniff her before attempting to touch them. Following this, your cat will undergo a gentle orthopaedic examination by Evelyn to detect the presence of joint pain. Evelyn may be accompanied by a student. Your cat will then wear an accelerometer, weighing 17g, on the breakaway collar for a total period of fourteen days, to measure their activity profile and sleep/rest patterns.

Who will hold my cat during the examination?
Our team are experienced with cats and will be able to complete the examination without assistance from you. However, if you would prefer to hold your cat, then this will be fine. We will take things carefully at your cat's pace, although holding your cat will be at your own risk.

What happens if my cat gets worried with any of the procedures?
If at any point you or Evelyn feel that your cat is becoming worried by the procedures (wearing a collar, home visit, orthopaedic examination, wearing an accelerometer), then the procedure will stop immediately. In the case of the orthopaedic examination, and only if you consent, Evelyn may wait for a few minutes to allow your cat further time to habituate to their presence and try again, depending on the individual circumstances.

What can I do to help?

It is helpful if other cats and dogs are kept out of the room when the visit takes place as they tend to want to 'join in'.

Hygiene
As part of our general hygiene practices, members of the study team will wear a clean veterinary top at each visit.

What are the possible disadvantages and risks of taking part?
One possible adverse effect is your cat becoming worried during or after the visits. To prevent this from happening, cats whose owners report that they are fearful of strangers will be excluded from the study. Evelyn will also allow your cat to acclimatise to their presence for at least 15 minutes before any handling and adhere to the principles of feline-friendly practice as detailed above.
Another possible risk would be strangulation as a result of wearing a collar. To prevent this from happening, a breakaway (safety) cat collar will be provided if your cat is not already wearing one, with collar introduction being a step by step process; we will provide you with instructions on how to do so and your cat will be given a minimum of seven days to acclimatise to wearing it.
As stated above, if at any point you or Evelyn feel that your cat is becoming worried by the procedures then the procedure will stop immediately. In the case of the orthopaedic examination, and only if you consent, Evelyn may wait for a few minutes to allow your cat further time to habituate to their presence and try again, depending on the individual circumstances.

What are the possible benefits of taking part?
Although there is no personal gain for you, the information gained from this study will help advance the knowledge of feline DJD and the environmental needs of indoor cats, both of which will improve their QoL.

What will happen if I do not want to carry on with the study?
You can withdraw from the study at any time without giving a reason. Any data we have collected from you and your cat during the course of the study will be destroyed.

Will my taking part in this study be kept confidential?
- Your participation in the study will be completely confidential to all except the researchers involved.
- All data collected from this study will be anonymised after collection, and no participants will be identifiable in resulting reports or publications.
- Data will be collected by accessing your cat's Bristol Cats and medical records, as well as during visiting your house.
- The data will be stored both in hard copy and electronic format and securely held at School of Veterinary Science, University of Bristol in accordance with the Data Protection Act 2018.
- The data will be retained for 10 years, following which it will be disposed of securely.

What will happen to the results of the research study?
You will be informed about the outcome of the study via social media and/or e-mail following study completion, depending on your preference. The study findings will be published in a peer review veterinary journal and/or presented at veterinary conferences, as well as in the Bristol Cats website, newsletter, and social media. You will not be identified in any report or publication.

Who is organising and funding the research?
The research is organised by Evelyn Maniaki at Bristol Veterinary School as part of her MSc, with her supervisory team listed at the header of the first page. The research has been funded by Zoetis UK Ltd.

Who has reviewed the study?
The study has been reviewed by University of Bristol's Health Sciences Faculty Research Ethics Committee (FREC) and the Animal Welfare and Ethical Review Body (AWERB).

Further information and contact details
Researcher contact details: Dr Evelyn Maniaki (evelyn.maniaki@bristol.ac.uk)

Supervisor contact details: Dr Emily Blackwell (emily.blackwell@bristol.ac.uk)

Bristol Veterinary School
Dolberry Building
Langford House
Langford
Bristol
BS40 5DU

Contact details for formal complaints: research-governance@bristol.ac.uk

APPENDIX J STUDY PARTICIPANT CONSENT FORM

University of BRISTOL

CONSENT FORM

Research project title: The impact of feline degenerative joint disease on mobility and quality of life in cats

Research investigator: Dr Evelyn Maniaki

Supervisors: Dr Emily Blackwell; Dr Jo Murrell; Professor Sorrel Langley-Hobbs

I agree that (*please check off and initial each section to which you agree*):

☑ INITIALS

☐ ☐ I have read and understood the information sheet dated 13/06/2018 for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐ ☐ I can ask any questions during the visit and may contact the researcher with any future questions.

☐ ☐ I am voluntarily taking part in this project and I am free to withdraw at any time without giving any reason.

☐ ☐ I do not expect to receive any benefit or payment from participation.

☐ ☐ I consent to the researcher contacting my vet and obtaining my cat's medical notes.

My Vet's details:

_____

☐ ☐ I understand that relevant sections of my cat's medical notes and data collected during the study may be looked at by individuals from the research project team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my cat's records.

☐ ☐ I consent for pictures of my cat being taken for use in reports and publications resulting from this study.

☐ ☐ I understand that anonymised data may be published under the conditions stated above.

☐ ☐ If I have any concerns about this research or the way it is being conducted, or if I wish to make a complaint, I may contact the Faculty of Health Sciences Ethical Committee.

☐ ☐ I agree to take part in the above study.

☐ ☐ I consent to be contacted by the Bristol Veterinary School for further research involving my cat.

_____	_____	_____
Printed name of participant	Date	Signature

_____	_____	_____
Printed name of researcher	Date	Signature

If you would like a copy of the publication of the results, please supply your email address:

_____

Evelyn Maniaki
FREEPOST RSHR-AGRJ-UABZ
Bristol Cats
University of Bristol
Dolberry Building
Langford
Bristol
BS40 5DU

Researcher contact details:

Dr Evelyn Maniaki: evelyn.maniaki@bristol.ac.uk

Supervisor contact details:

Dr Emily Blackwell: emily.blackwell@bristol.ac.uk

Bristol Veterinary School
Langford House
Langford
Bristol
BS40 5DU

Contact details for formal complaints:

research-governance@bristol.ac.uk

APPENDIX K ONLINE FELINE MUSCULOSKELETAL PAIN INDEX QUESTIONNAIRE

Feline Activity Study Questionnaire

Page 1: Feline Activity Study

Thank you for taking the time to participate in our study.

Completing the questionnaire should be straightforward and take less than 10 minutes.

Please let us know if you have any questions before or during completing this questionnaire.

Basic information about you and your cat

E-mail address * *Required*

Your name * *Required*

Your cat's name

1 / 7

What is your cat's date of birth (exact or approximate)?

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

(dd/mm/yyyy)

What is your cat's breed?

What is your cat's gender?

- Male
- Female

Is your cat neutered (desexed)?

- Yes
- No

Does your cat have outside access, excluding going out into an enclosed 'run' or on a lead?

- Yes
- No

Please use this space to provide further details of your cat's outdoor access, if applicable.

During the last 12 months, has your cat had any problems that have led to veterinary visits?

- Yes
- No

Please use this space to provide further details of problems that have led to veterinary visits. If a vet has made a diagnosis, please include this information.

During the last 12 months, has your cat had any problems which you felt were not serious enough to seek veterinary attention for?

- Yes
- No

Please use this space to provide further details of problems that you felt were not serious enough to seek veterinary attention for.

Is your cat on any medication or supplements, excluding routine flea/worming treatment?

- Yes
- No

Please provide details of any medication or supplements, excluding flea/worming treatment, that your cat is receiving / has received over the last 6 months. This should include name of medication, dose, frequency administration and date started/finished (or course length).

Are you happy for your cat to wear a breakaway (safety) cat collar with the attached accelerometer for a short period of time? Don't worry if your cat isn't wearing one already, this can be provided along with step by step instructions of how to slowly introduce your cat to it.

- Yes
- No

Page 2: Your cat's mobility

Please choose the answer that best describes your cat's ability to perform the following activities as compared to what you think a **normal** adult cat, without mobility impairment, would be able to do.

	Normal	Not quite normal	Moderately worse than normal	Barely, with great effort	Not at all	Not applicable
1. Walk and / or move easily?	○	○	○	○	○	○
2. Run?	○	○	○	○	○	○
3. Jump up (how well and how easily)?	○	○	○	○	○	○
4. Jump up to kitchen-counter height in one try?	○	○	○	○	○	○
5. Jump down (how well and how easily)?	○	○	○	○	○	○
6. Climb up stairs or steps?	○	○	○	○	○	○
7. Go down stairs or steps?	○	○	○	○	○	○
8. Play with toys and / or chase objects?	○	○	○	○	○	○
9. Play and interact with other pets?	○	○	○	○	○	○
10. Get up from a resting position?	○	○	○	○	○	○
11. Lie and / or sit down?	○	○	○	○	○	○
12. Stretch?	○	○	○	○	○	○
13. Groom himself / herself?	○	○	○	○	○	○

14. Interact with you and family members?	○	○	○	○	○	○
15. Tolerate being touched and / or held?	○	○	○	○	○	○
16. Eat?	○	○	○	○	○	○
17. Use the litter box (get in and out, squat, cover waste)?	○	○	○	○	○	○

Page 3: Thank you very much for your help!

Thank you very much for completing this questionnaire!

We really appreciate the time that you have taken to complete this questionnaire to tell us about your cat. The information you give us about your cat will help us to help cats in the future.

If you have any questions, please contact Dr Evelyn Maniaki by:

e-mail: cat-study@bristol.ac.uk

phone: 07827 981412

post: Bristol cats (FREEPOST RSHR-AGRJ-UABZ) Dr Emily Blackwell, University of Bristol, Langford House, Langford, North Somerset, BS40 5DU

https://www.facebook.com/feline.activity.study/

APPENDIX L ONLINE VETMETRICA QUESTIONNAIRE

Feline Activity Study Questionnaire – Quality of Life assessment

Page 1: Feline Activity Study

Thank you for taking the time to participate in our study.

Completing the questionnaire should be straightforward and take less than 10 minutes.

Please let us know if you have any questions before or during completing this questionnaire.

Information about you and your cat

E-mail address *Required*

Your name *Required*

Your cat's name

Page 2: Your cat's quality of life

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Active *(Engaging or ready to engage in physically energetic pursuits)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 3: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Unsteady *(Liable to fall or shake, not steady in position)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 4: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Energetic *(Showing great activity or vitality)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 5: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Comfortable *(Free from discomfort; at ease)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 6: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Lethargic *(Affected by lethargy; sluggish and showing or feeling no interest or enthusiasm)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 7: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Showing hunting behaviour *(Actively hunting prey, pouncing; stalking; chasing or play-attacking toys)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 8: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Lively *(Full of energy and enthusiasm)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 9: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Alert *(Attentive; watchful or vigilant)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 10: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Sore *(Suffering pain from a part of one's body)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 11: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Content *(In a state of peaceful happiness)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 12: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Playful *(Fond of games and amusement)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 13: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Uncomfortable *(Feeling slight pain or physical discomfort)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 14: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Enjoying the things, he / she usually does *(Engaging in usual behaviour and activity fully, deriving pleasure from usual activities)*

- 6 - Could not be enjoying them more
- 5
- 4
- 3
- 2
- 1
- 0 - Not enjoying them at all

Page 15: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Jumping or climbing up / down as usual *(Jumping or climbing up/down to the things/heights and in the ways that are usual for your cat)*

- 6 - Couldn't be jumping or climbing up / down more
- 5
- 4
- 3
- 2
- 1
- 0 - Not jumping or climbing up / down at all

Page 16: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Exploring *(Engaging with environment or surroundings frequently; patrolling)*

- 6 - Couldn't be exploring more
- 5
- 4
- 3
- 2
- 1
- 0 - Not exploring at all

Page 17: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Feeling himself / herself *(Being in his/her usual frame of mind or state of health)*

- 6 - Couldn't be feeling more himself / herself
- 5
- 4
- 3
- 2
- 1
- 0 - Not feeling himself / herself at all

Page 18: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Stiff *(Unable to move easily and without pain)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 19: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Happy *(Feeling or showing pleasure or contentment)*

- 6 - Couldn't be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 20: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Inquisitive *(Having or showing an interest in things; curious)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 21: Your cat's quality of life - continued

Please think about how your cat is behaving today and use the scale to tell us how well the phrase describes your cat or what he/she is doing.

Slow *(Behaving in a slow manner; moving or operating at a low speed; not quick or fast)*

- 6 - Could not be more
- 5
- 4
- 3
- 2
- 1
- 0 - Not at all

Page 22: Your cat's quality of life - continued

And, finally, how would you rate your cat's quality of life?

- Very good
- Good
- Poor
- Very poor

Page 23: Thank you very much for your help!

Thank you very much for completing this questionnaire!

We really appreciate the time that you have taken to complete this questionnaire to tell us about your cat. The information you give us about your cat will help us to help cats in the future.

If you have any questions, please contact Dr Evelyn Maniaki by:

e-mail: cat-study@bristol.ac.uk

phone: 07827 981412

post: Bristol cats (FREEPOST RSHR-AGRJ-UABZ) Dr Emily Blackwell, University of Bristol, Langford House, Langford, North Somerset, BS40 5DU

https://www.facebook.com/feline.activity.study/

APPENDIX M ORTHOPAEDIC EXAMINATION SHEET

DJD ID:	OWNER NAME:	CAT NAME:

	RIGHT LIMB								LEFT LIMB								SPINE			
	MAN	CAR	ELB	SHO	PES	TAR	STIF	HIP	MAN	CAR	ELB	SHO	PES	TAR	STIF	HIP	CER	THOR	LUM	LS
PAIN																				
CREPITUS																				
EFFUSION																				
THICKENING																				

BODY CONDITION SCORE:	
TEMPERAMENT SCORE:	

PAIN SCORE (APPENDICULAR & AXIAL SKELETON)	
0	No resentment
1	Mild withdrawal; mildly resists
2	Moderate withdrawal; body tenses; may orient to site; may vocalize/increase in vocalization
3	Orients to site; forcible withdrawal from manipulation; may vocalize or hiss or bite
4	Tries to escape/prevent manipulation; bite/hiss; marked guarding of area

CREPITUS, THICKENING AND EFFUSION SCORE (APPENDICULAR SKELETON ONLY)	
0	None
1	Slight – moderate
2	Severe

TEMPERAMENT SCORE	
0	Neutral attitude, purring, kneading
1	Resistance to restraint
2	Resistance to restraint, growling and hissing
3	Resistance with biting and scratching, hissing, spitting, and vocalising
4	Resistance with biting, scratching, hissing, spitting, vocalising, urinating or defaecating

APPENDIX N ACCELEROMETER OWNER DIARY

Feline Activity Study – Accelerometer Diary

Write "OK" within the box when both the collar and the accelerometer stayed on your cat without any issues. Alternatively, if the collar and/or the accelerometer were off your cat for a period of time, no matter how brief that was, please indicate which piece of equipment came off, what time you discovered it and what time you put it back on again. Thank you for participating in this exciting study!

DATE	COMMENTS

APPENDIX O TESTS OF NORMALITY AND TRANSFORMATIONS

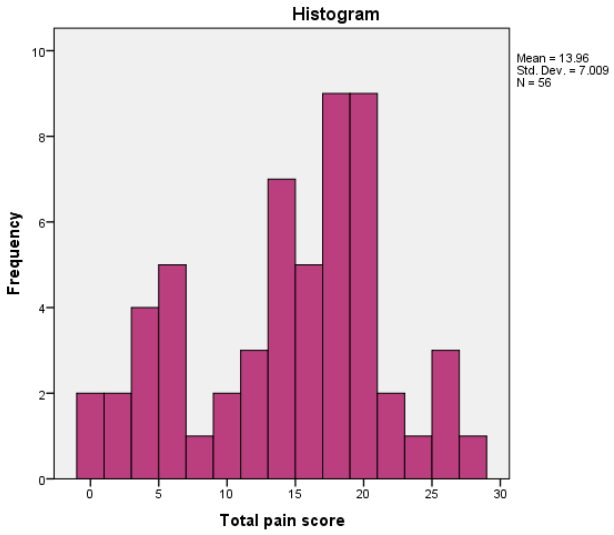
Tests of Normality and Histograms for Continuous Variables

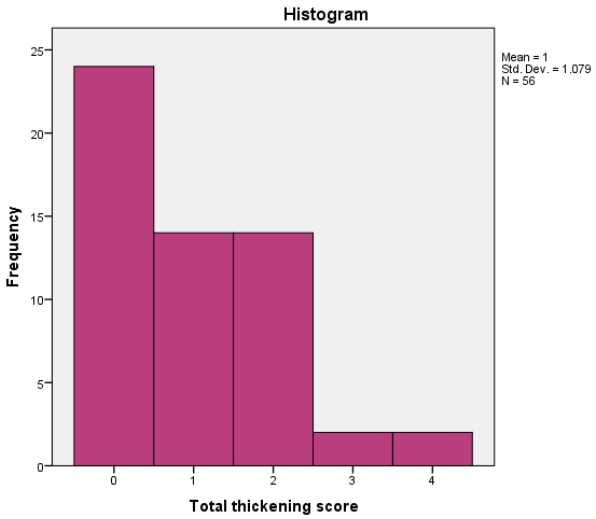
Tests of Normality

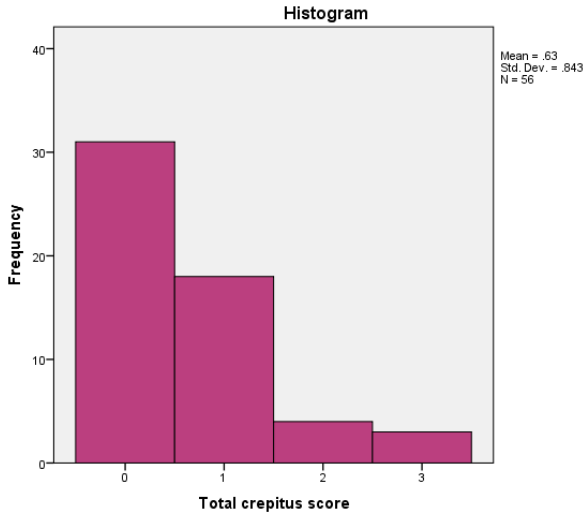
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Total pain score	.114	56	.067	.952	56	.027
Total thickening score	.252	56	.000	.819	56	.000
Total crepitus score	.324	56	.000	.724	56	.000
Feline Musculoskeletal Pain Index	.244	56	.000	.713	56	.000
Vitality domain	.068	56	.200*	.973	56	.234
Comfort domain	.173	56	.000	.902	56	.000
Emotional Wellbeing domain	.147	56	.004	.904	56	.000
Number of joints with bilateral disease	.187	56	.000	.915	56	.001

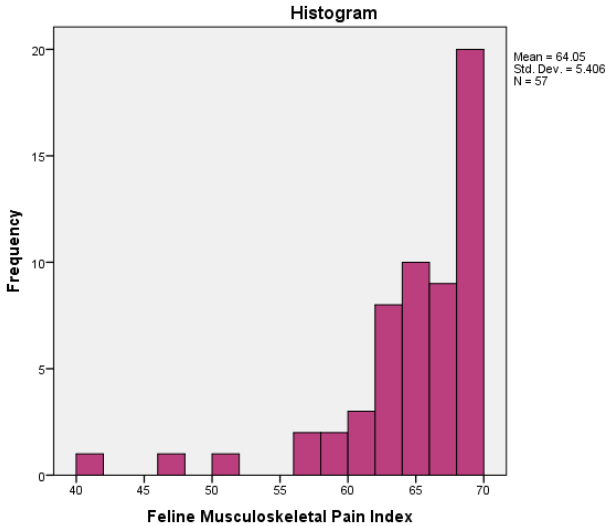
*. This is a lower bound of the true significance.

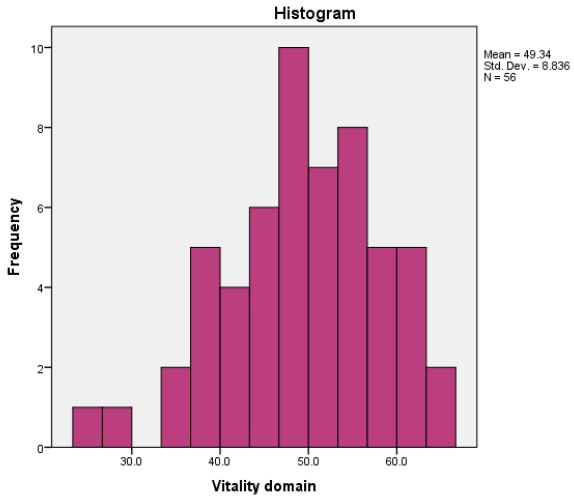
a. Lilliefors Significance Correction

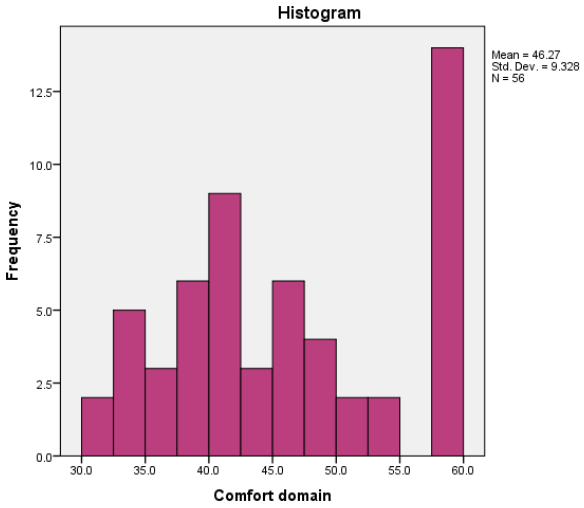


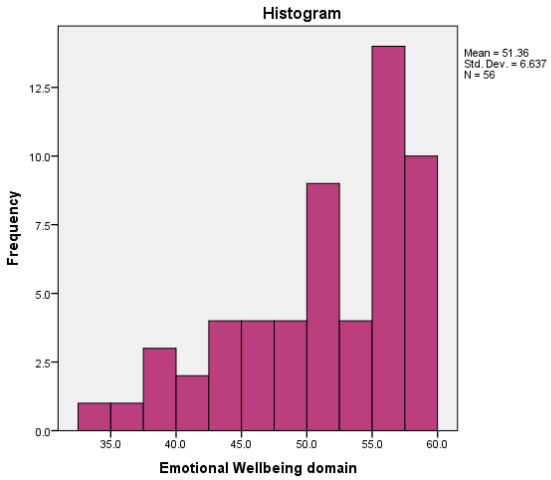

Histogram
Mean = 1
Std. Dev. = 1.079
N = 56
Frequency
Total thickening score

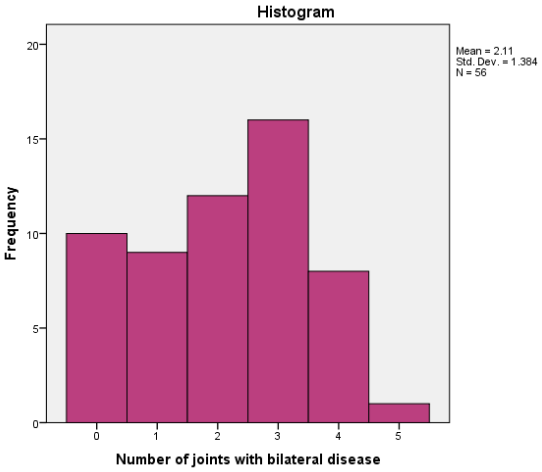

Histogram
Mean = .63
Std. Dev. = .843
N = 56
Frequency
Total crepitus score


Histogram
Mean = 64.05
Std. Dev. = 5.406
N = 57
Frequency
Feline Musculoskeletal Pain Index


Histogram
Mean = 49.34
Std. Dev. = 8.836
N = 56
Frequency
Vitality domain


Histogram
Mean = 46.27
Std. Dev. = 9.328
N = 56
Frequency
Comfort domain


Histogram
Mean = 51.36
Std. Dev. = 6.637
N = 56
Frequency
Emotional Wellbeing domain



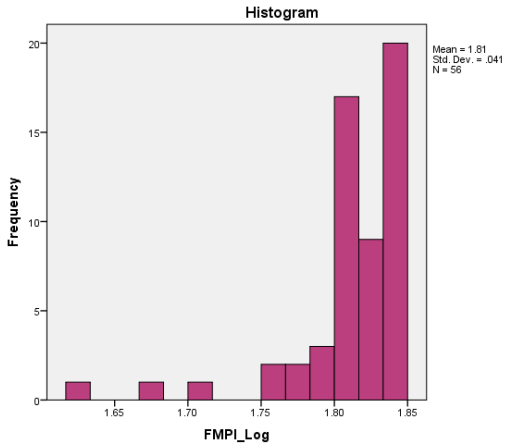
Data Transformation for Non-normally Distributed Continuous Variables

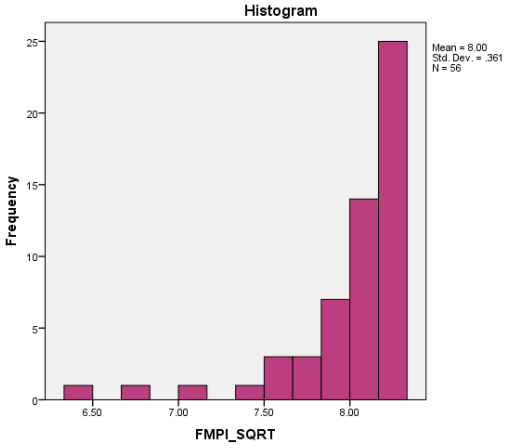
Tests of Normality

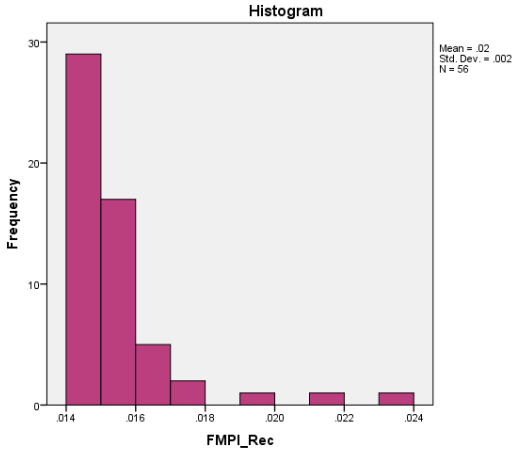
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
FMPI_Log	.269	56	.000	.663	56	.000
FMPI_SQRT	.256	56	.000	.688	56	.000
FMPI_Rec	.293	56	.000	.606	56	.000
QoL_Com_Log	.162	56	.001	.924	56	.002
QoL_Com_SQRT	.168	56	.000	.915	56	.001
QoL_Com_Rec	.148	56	.004	.933	56	.004
QoL_EWB_Log	.150	56	.003	.883	56	.000
QoL_EWB_SQRT	.149	56	.003	.894	56	.000
QoL_EWB_Rec	.166	56	.001	.854	56	.000
T_Thickening_Log	.281	56	.000	.819	56	.000
T_Thickening_SQRT	.289	56	.000	.803	56	.000
T_Thickening_Rec	.295	56	.000	.766	56	.000
T_Crepitus_Log	.349	56	.000	.748	56	.000
T_Crepitus_SQRT	.356	56	.000	.739	56	.000
T_Crepitus_Rec	.361	56	.000	.723	56	.000
Bilat_Sum_Log	.228	56	.000	.846	56	.000
Bilat_Sum_SQRT	.236	56	.000	.825	56	.000
Bilat_Sum_Rec	.299	56	.000	.720	56	.000

a. Lilliefors Significance Correction

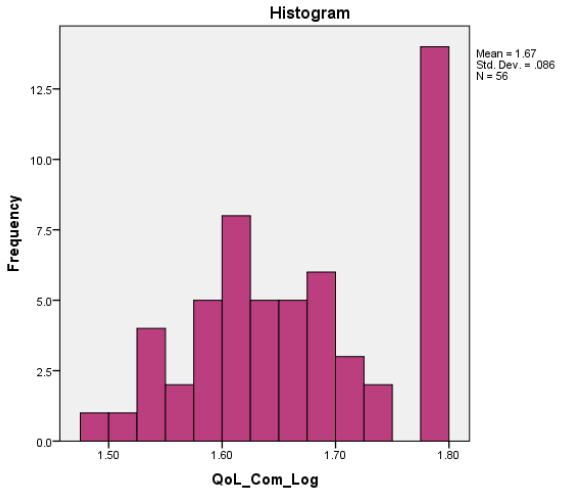
Feline Musculoskeletal Pain Index

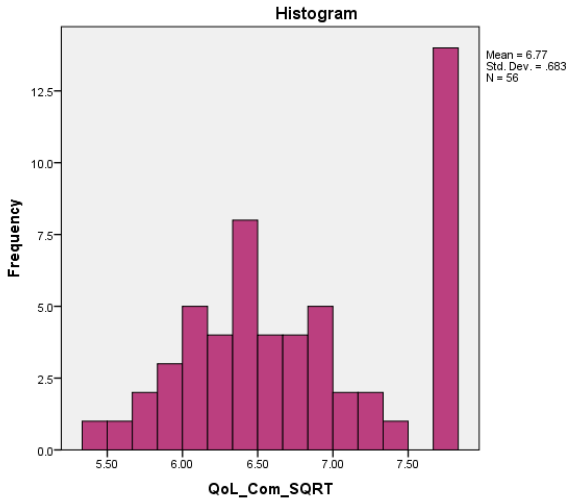


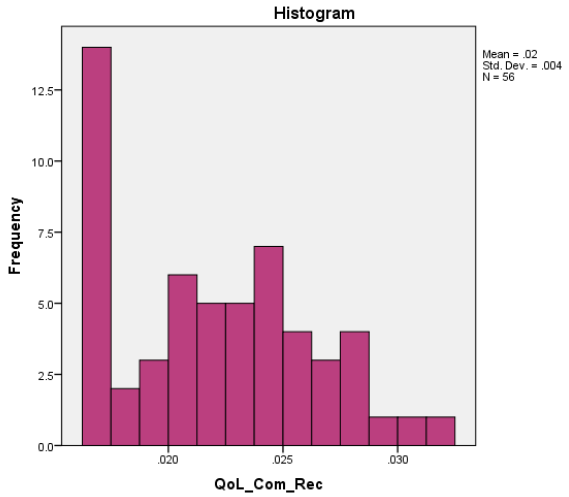




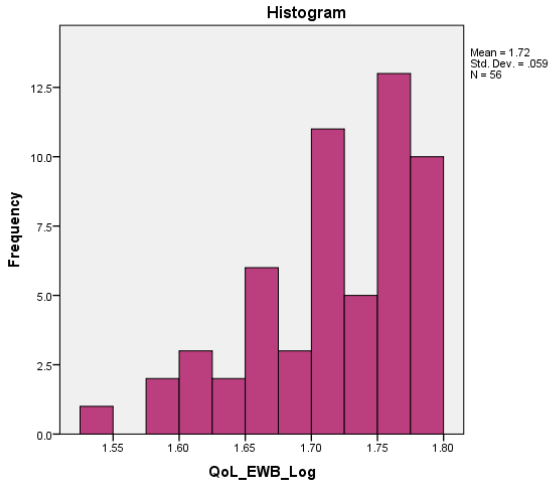
VetMetrica Comfort Domain Score

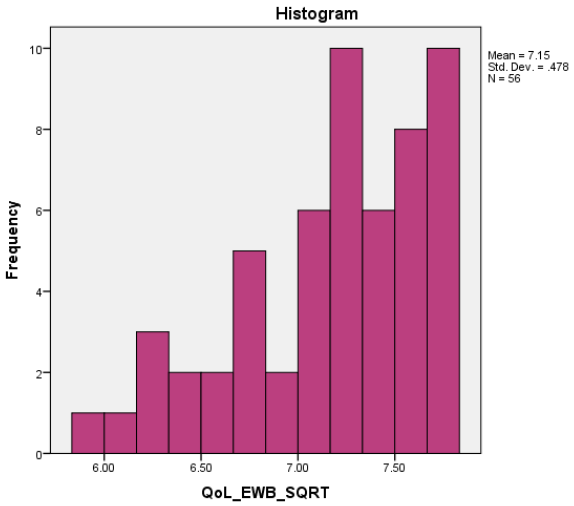


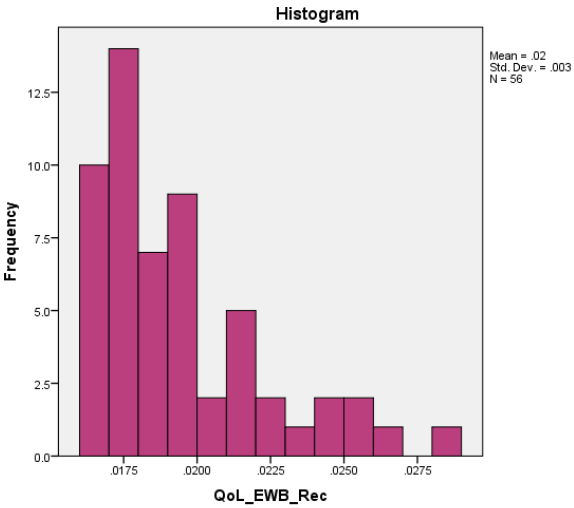




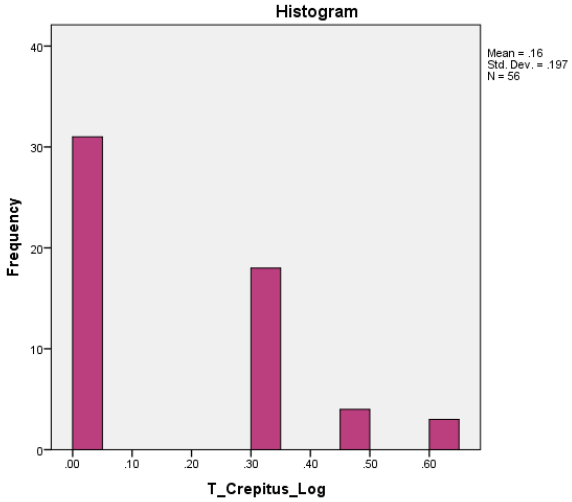
VetMetrica EWB Domain Score

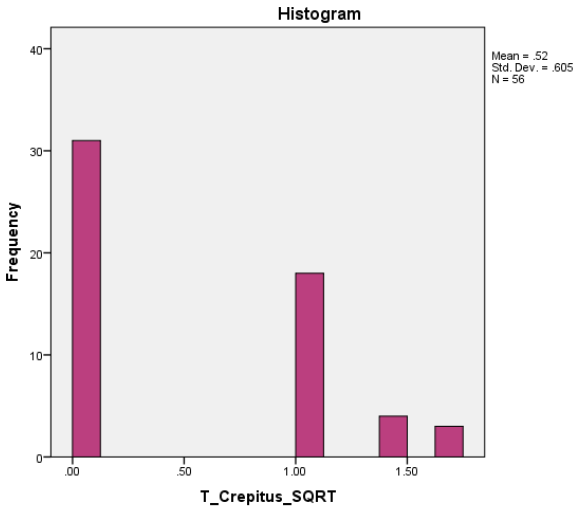


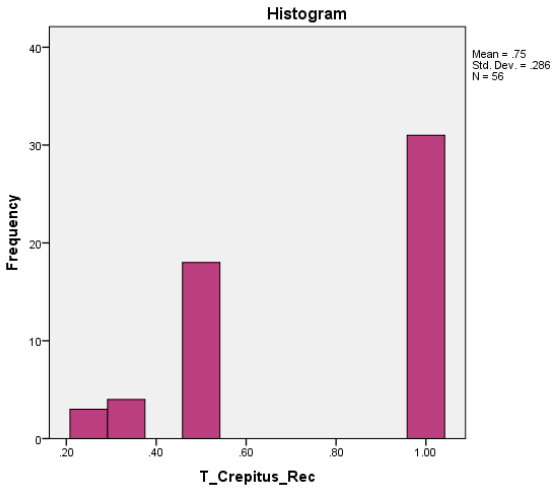




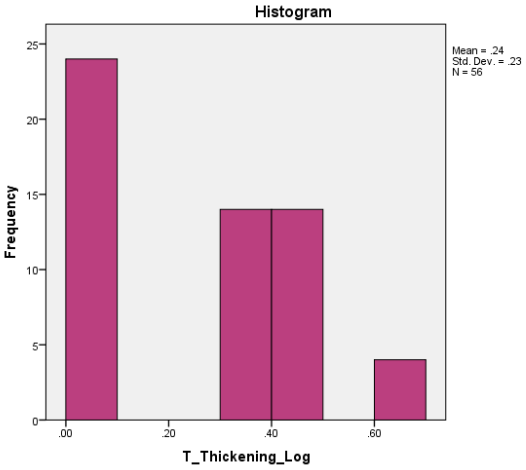
Total Crepitus Score

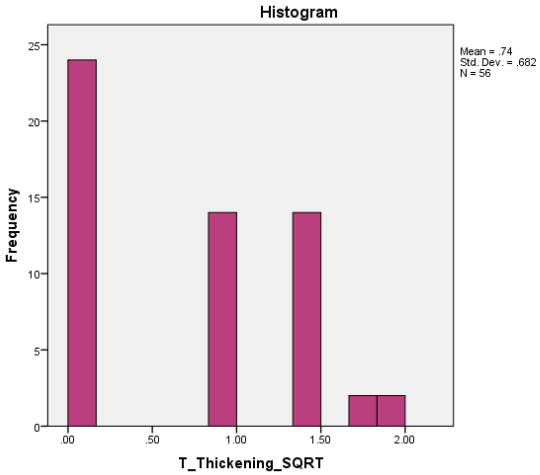


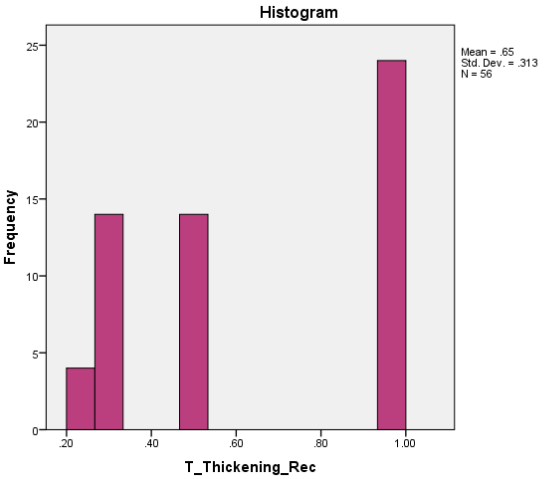




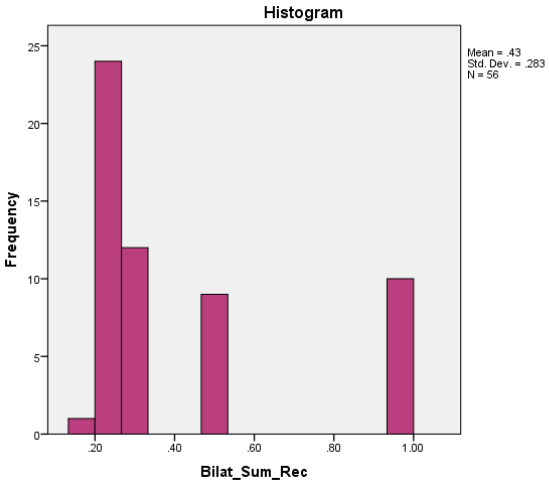
Total Thickening Score

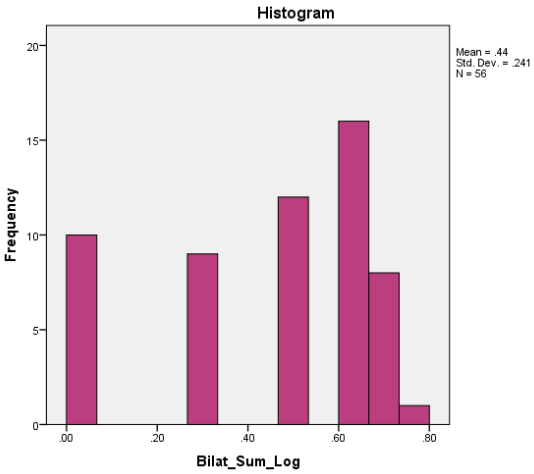


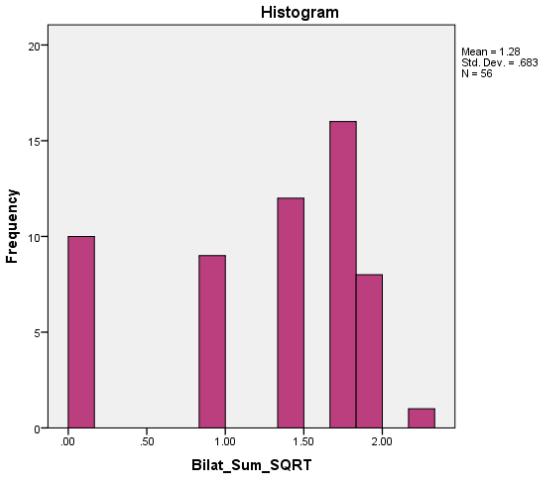




Number of Joints with Bilateral Pain







APPENDIX P HOLM-BONFERRONI METHOD CALCULATIONS

Holm-Bonferroni formula for each p-value: $\alpha / (n - \text{rank} + 1)$

Hypothesis-associated Variable	p-value	Rank	Corrected p-value	Reject Null Hypothesis?
Total Pain score	0.0001	1	0.0036	Yes
Number of joints affected with bilateral disease	0.001	2	0.0038	Yes
VetMetrica Comfort Domain score	0.002	3	0.0042	Yes
Total Crepitus score	0.002	4	0.0045	Yes
Feline Musculoskeletal Pain Index	0.003	5	0.0050	Yes
Total Thickening score	0.003	6	0.0056	Yes
Prevalence of Bilateral Pain	0.005	7	0.0063	Yes
VetMetrica Vitality Domain score	0.009	8	0.0071	No
VetMetrica Emotional Wellbeing Domain score	0.018	9	0.0083	No
Age in Life Stages	0.079	10	0.0100	No
Sex	0.11	11	0.0125	No
Temperament	0.258	12	0.0167	No
Body Condition Score (assessed by veterinary surgeon)	0.425	13	0.0250	No
Breed category	0.765	14	0.0500	No

APPENDIX Q ACCELEROMETER MISSING DATA POINTS

DJD ID	Start of Recording (Date and Time)	End of Recording (Date and Time)	Total Recording Duration (Start to End)	Duration of Device Not on Cat (minutes)	Proportion that Device Remained on Cat
11	13/02/2019 08:00:00	26/02/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
12	05/12/2018 08:00:00	17/12/2018 08:00:00	12 days 0 hrs 0 mins	1020	94.10%
13	13/03/2019 08:00:00	25/03/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
24	16/01/2019 08:00:00	29/01/2019 11:00:00	13 days 3 hrs 0 mins	0	100.00%
26	01/03/2019 08:00:00	13/03/2019 08:00:00	12 days 0 hrs 0 mins	480	97.22%
31	06/12/2018 08:00:00	18/12/2018 08:00:00	12 days 0 hrs 0 mins	0	100.00%
36	12/04/2019 08:00:00	24/04/2019 08:00:00	12 days 0 hrs 0 mins	867	94.98%
40	11/12/2018 08:00:00	23/12/2018 08:00:00	12 days 0 hrs 0 mins	0	100.00%
57	22/02/2019 08:00:00	06/03/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
75	13/02/2019 08:00:00	26/02/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
77	16/01/2019 08:00:00	29/01/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
78	06/02/2019 08:00:00	19/02/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
128	22/02/2019 08:00:00	06/03/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
129	26/03/2019 08:00:00	08/04/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
600	16/12/2018 08:00:00	28/12/2018 08:00:00	12 days 0 hrs 0 mins	0	100.00%
601	08/03/2019 08:00:00	20/03/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
602	08/03/2019 08:00:00	20/03/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
603	20/03/2019 08:00:00	02/04/2019 10:30:00	13 days 2 hrs 30 mins	0	100.00%
604	27/03/2019 08:00:00	08/04/2019 07:00:00	11 days 23 hrs 0 mins	60	99.65%
605	28/03/2019 08:00:00	09/04/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
607	09/04/2019 08:00:00	21/04/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
608	22/05/2019 08:00:00	05/06/2019 08:00:00	14 days 0 hrs 0 mins	0	100.00%
609	14/05/2019 08:00:00	27/05/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
610	08/05/2019 08:00:00	19/05/2019 08:00:00	11 days 0 hrs 0 mins	0	100.00%

611	19/04/2019 08:00:00	02/05/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
612	14/06/2019 08:00:00	26/06/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
613	22/05/2019 08:00:00	05/06/2019 08:00:00	14 days 0 hrs 0 mins	0	100.00%
614	13/04/2019 08:00:00	25/04/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
618	10/10/2019 08:00:00	23/10/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
619	18/07/2019 08:00:00	30/07/2019 07:00:00	11 days 23 hrs 0 mins	0	100.00%
620	01/08/2019 08:00:00	14/08/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
621	19/07/2019 08:00:00	31/07/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
622	19/07/2019 08:00:00	31/07/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
623	29/06/2019 08:00:00	12/07/2019 23:30:00	13 days 15 hrs 30 mins	8940	48.35%
626	12/06/2019 08:00:00	26/06/2019 08:00:00	14 days 0 hrs 0 mins	0	100.00%
627	27/06/2019 08:00:00	10/07/2019 08:00:00	13 days 0 hrs 0 mins	60	99.68%
630	31/07/2019 08:00:00	13/08/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
631	29/08/2019 08:00:00	11/09/2019 07:00:00	12 days 23 hrs 0 mins	0	100.00%
632	13/09/2019 08:00:00	25/09/2019 12:00:00	12 days 4 hrs 0 mins	5	99.97%
634	18/07/2019 08:00:00	30/07/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
635	28/06/2019 08:00:00	14/07/2019 08:00:00	16 days 0 hrs 0 mins	5	99.98%
637	02/08/2019 08:00:00	12/08/2019 12:30:00	10 days 4 hrs 30 mins	1440	90.00%
642	03/10/2019 08:00:00	16/10/2019 12:30:00	13 days 4 hrs 30 mins	180	99.04%
645	31/08/2019 08:00:00	12/09/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
646	15/08/2019 08:00:00	28/08/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
647	30/08/2019 08:00:00	11/09/2019 10:00:00	12 days 2 hrs 0 mins	0	100.00%
648	01/08/2019 08:00:00	14/08/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
649	16/08/2019 08:00:00	28/08/2019 08:00:00	12 days 0 hrs 0 mins	60	99.65%
650	16/08/2019 08:00:00	28/08/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
651	12/09/2019 08:00:00	25/09/2019 11:30:00	13 days 3 hrs 30 mins	0	100.00%
652	12/09/2019 08:00:00	25/09/2019 11:30:00	13 days 3 hrs 30 mins	0	100.00%

655	31/08/2019 08:00:00	12/09/2019 08:00:00	12 days 0 hrs 0 mins	0	100.00%
658	24/10/2019 08:00:00	06/11/2019 08:00:00	13 days 0 hrs 0 mins	0	100.00%
660	02/10/2019 08:00:00	13/10/2019 20:00:00	11 days 12 hrs 0 mins	0	100.00%
661	25/10/2019 08:00:00	06/11/2019 09:00:00	12 days 1 hrs 0 mins	0	100.00%
662	24/10/2019 08:00:00	06/11/2019 12:00:00	13 days 4 hrs 0 mins	20	99.89%